PHYSICAL FITNESS, DIET AND EXERCISE

Exercise

Physical, Physiological and Psychological Benefits

Dulce Esteves • Kiara Lewis
Editors

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PHYSICAL FITNESS, DIET AND EXERCISE

EXERCISE

PHYSICAL, PHYSIOLOGICAL AND PSYCHOLOGICAL BENEFITS

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DULCE ESTEVES
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KIARA LEWIS
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Medicine & Health
New York

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PREFACE

The book "Exercise: Physical, Physiological and Psychological Benefits" was an initiative of the publishing program of Nova Science Publishers, Inc.

The publisher was looking for state of the art, global insights on the benefits of physical activity on different domains of health and wellbeing. Accordingly, the publisher invited investigators with previous research on the area, to contribute to a global, integrated, vision on the major benefits and potentialities, including exercise characteristics and training specifications, in order to act as a stimulus that promotes physiological adaptations that may prevent or retard different pathologies.

Fortunately, several investigators around the world found the book theme interesting, and decide to contribute some of their research, proposing a book chapter. From those contributions, editors choose the chapters that not only fit the books' general goal, but also that provide the greatest variety of subjects related to the main issue. As a result, this book presents chapters related to emotional and psychological benefits of exercise, role of exercise in insulin regulation, benefits of exercise in conditions such as fibromyalgia, oncologic disease, rheumatic inflammatory diseases, polycystic ovary syndrome or oral health. Additionally, some chapters focus on the importance of exercise in dementia, mental health or children diagnosed with autism spectrum disorders. Potentialities of aquatic exercise for health were also addressed.

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When analysing all proposed chapters, the two editors acknowledge the remarkable diversity of the research topics, scientific areas, methodologies and approaches. We were able to gather contributions from seven different countries and five continents. This worldwide contribution emphasises the global perspective of the book.

Developed within a base of scientific accuracy and precision, this book aims to accomplish a general synthesis of the topics covered, so that it can be a scientific dissemination book for students and professionals in the field of fitness, who seek to update their scientific knowledge about the benefits of exercise in different areas of health, as well as the type of exercise that should be performed to prevent and manage different pathologies, but who are not readers of scientific journals. Therefore, this book is a must read for fitness professionals, sport scientists, sports students, and for anyone who wants to deepen their knowledge about the benefits of exercise in different pathologies, and in health in general.

During the period the book was completed, two approaches should be highlighted: (1) the great cooperation and affinity that emerged from editors - all decisions were made with all accordance, and the editors participated on the project with all resources they had; (2) the extraordinary collaboration of all authors in revising the chapters, with the purpose of making the book a more coherent final product.

The editors must send thanks to Nova Science Publishers, Inc. for all the support during the writing and editing process, particularly to Aleksandra Bator, who always supported our work.

Covilhã, Portugal, Gloucestershire, UK
Dulce Esteves Kiara Lewis

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Chapter 1

PHYSICAL EXERCISE: EMOTIONAL AND PSYCHOLOGICAL BENEFITS

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ABSTRACT

Regular physical exercise has been demonstrated to play an important role in coping with stress and as a factor in improving a person's quality of life. There is extensive literature indicating the benefits of psychical exercise in different areas of psychological wellbeing: it increases subjective health and mood, reduces depression and levels of anxiety and stress and improves self-esteem. Moreover, it is also important to study the emotional impact of physical exercise. There is a vast literature base on negative emotions and the maladjustment of emotional regulation showing that this type of emotion may lead to a decrease in physical exercise. However, there is much less research about physical exercise and its relationship with positive emotions.

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The aims of this chapter will be to describe and analyze the existing relationships between emotional and psychological variables and physical exercise.

It will describe three studies that evaluate emotions, psychological variables and physical exercise. The methodology of the three studies is descriptive, correlational and cross-sectional. The results in the three studies will be described. In sum, results show that people who do physical exercise have high optimism, happiness, resilience, self-esteem, psychological well-being and emotional intelligence.

At the end of the chapter will be written general conclusions about physical exercise and emotional and psychological benefits.

Keywords: physical exercise, emotions, psychological benefits

INTRODUCTION

Research on individuals' health has focused part of its efforts on trying to mitigate the problems arising from sedentarism through physical exercise, following the recommendations proposed by the World Health Organization (WHO, 2010), among others. Scientists are concerned about providing citizens with strategies that foster healthy lifestyle habits. Therefore, they have devoted much of their efforts to determine the effects of regular physical exercise on health, stressing that its practice is essential to prevent, and even effectively combat, some diseases (Rhodes, Janssen, Bredin, Warburton and Bauman, 2017). Specifically, the adult population is recommended to perform 150 minutes per week of moderate-intensity aerobic physical activity or 75 minutes of vigorous aerobic physical activity each week (WHO, 2020).

Among other benefits, the practice of regular exercise helps to reduce obesity (Okay et al., 2009; Swift, et al., 2018), control diabetes (Turner, et al., 2019), mitigate osteoporosis (Snow, Shaw, Winters, and Witske, 2000), reduce fatigue and pain in people with fibromyalgia (Busch et al., 2011), or positively affect the cardiopulmonary function (Chan et al., 2013). Evidence of the benefits for mental health (Chekroud, et al., 2019; Sharma et al., 2006) and emotional states (Salovey et al., 2000; Stolarska et al., 2019) has also been described in

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addition to revealing a reduced risk of depression (Craft & Perna, 2004) and improved psychological well-being (Tweed, et al., 2020; Zubala et al., 2017).

On the other hand, sport is defined as an exercise that follows rules and regulations in order to compete and award prizes to the best athletes or teams (Rosselli, pp.6, 2018). Emotions have been studied in sport performance as a classic subject of Sports Psychology (Ekkekakis, 2012). Athletes' emotions play an important role in their athletic performance and information processing (Stanger et al., 2018). Thus, there is evidence that the effects of some negative emotions, such as anxiety about competitions, can deteriorate athletic performance (Morillo et al., 2016). The main focus of the study of athletes' emotions has been the different negative emotions that they may experience, given the enormous consequences that this can have for their sporting life or subsequently, such as depression after suffering an injury or at the end of their sporting career (Sanders & Stevinson, 2017).

However, there is insufficient scientific research on positive emotions and their impact on athletic performance (Laborde et al., 2011; McCarthy, 2011). Athletes seem prepared to face a multitude of obstacles during their sporting practice: they face daily hard hours of training, working under pressure, harsh criticism, the daily demand for results, and even coping with their own negative emotions, which undoubtedly impair their performance, achievement, and sports performance. To overcome all these daily adversities, athletes must focus their resources and strengths on the enhancement of positive emotions, seeking well-being, and be capable of regulating their negative emotions. Logically, this entails another challenge added to the psychological preparation for their sport. They must also observe the coaches' emotions shown through their expressions of happiness or anger, which influence the athletes' performance (van Kleef et al., 2019). Therefore, athletes' well-being and its reflection in sporting performance seems to be influenced by many aspects.

Research from the psychology of sports has not differentiated between global well-being and well-being in the sports context, which has hindered its research (Lundqvist, 2011), noting that over the past decade there has been a significant increase in research addressing

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well-being in the context of sport as evidenced by the results of articles indexed in specialized sport databases. Athletes describe subjective well-being as an interaction of the following elements: satisfaction with life and sport, perceived health coupled with the happiness and pleasure they feel in the sport setting and in their ordinary life (Lundqvist and Sandin, 2014). The participation of young people in sports clubs positively influences them, extrapolating their mental and physical conditions in the sporting context to other contexts (Gísladóttir et al., 2013).

Emotional regulation has enormous value for the promotion of young athletes' well-being due to its mediating role between the perceived climate of care and mental well-being (Fry et al., 2012). Among the positive emotions studied are happiness, optimism, emotional intelligence, well-being, etc. Happiness in sports has been studied in extreme sports, among others, (Hetland et al., 2018), obtaining results that link greater participation in sports with a higher probability of experiencing happiness, coupled with a lower probability of socio-emotional difficulties (Booker et al., 2015). Concerning optimism, a systematic review (Ortín-Montero et al., 2018) indicated that optimism was linked to an increase in athletic performance. Similarly, a systematic review of the construct of emotional intelligence in athletes and physical activities (Laborde et al., 2016) found that in the sporting context, emotional intelligence is related to emotions, psychological stress responses, and better sports performance. In the context of physical activity, it was found that emotional intelligence was related to higher levels of physical activity and positive attitudes towards such activity.

Taking into account these variables, intervention programs have been developed for athletes, for example, for their development of a dual career, which has improved their self-efficacy and psychological well-being (Laureano et al., 2014). Some of the intervention programs with athletes, focusing on positive variables such as emotional intelligence, have also shown feasible benefits (Cece, et al., 2019). Others, focusing on yoga exercise and mindfulness among other aspects, have been shown to be effective in improving participants' self-esteem and happiness (Yook et al., 2017). However, despite all the advances in this field, studies on the relationships between positive

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emotions and the performance of physical exercise and sports remain scarce.

The aim of the chapter will be to describe and analyze the existing relationships between some positive emotional and psychological variables in people who take part in physical exercise or sport.

In the following part of the chapter, three studies will be described that evaluate positive emotions, psychological variables, and physical exercise. The methodology of the three studies was descriptive, correlational, and cross-sectional. The three study designs were approved by the Ethics Committee of the University.

In each study, the procedure, participants, variables, and instruments used, statistical analyses performed, and results obtained will be described. Finally, a discussion section, common to all three studies, will be presented.

STUDY 1

Method

Procedure and Participants

A convenience sample of 111 undergraduate students completed all the questionnaires. Of them, 97 were amateur athletes, 14 were not athletes. Of the amateur athletes, 64 were male, and 33 were female. Mean age was 22.8 years (*SD* = 7.04) and they practiced for an average number of practice days per week was 4.2 days (*SD* = 1.03).

Variables and Instruments

To evaluate psychological well-being, affect, optimism, and happiness the following questionnaires were used:

Psychological well-being was measured with the Ryff's Psychological Wellbeing Scales (PWB, Ryff, 1989). In this study the Spanish version was used (Díaz et al. 2006). It consists of 39 items rated on a 6-point Likert scale ranging from 1 (*totally disagree*) to 6 (*totally agree*). Items in this questionnaire are classified into 6 subscales that measure Self-Acceptance, Positive Relationships with

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others, Autonomy, Environmental Mastery, Purpose in Life, and Personal Growth. The internal consistency coefficients of the subscales ranged from .74 to .86. In this study, we calculated the total score of the scale (the sum of all items), which had an internal consistency coefficient of .94. Higher scores indicate higher psychological well-being.

Affect was measured with the Spanish version of the Positive Affect and Negative Affect Scale (PANAS; Sandín et al., 1999; Watson et al., 1988). It is composed of 20 items rated on a 5-point response scale ranging from 1 (*not at all*) to 5 (*very much*). Ten items refer to Positive Affect (e.g., “happy”, “positive”, “optimistic”) and 10 to Negative Affect (e.g., “angry”, “frustrated”, “annoyed”). Cronbach’s alpha was adequate for both subscales (.76 for Positive Affect and .73 for Negative Affect).

Optimism was assessed with the LOT-R (Scheier et al., 1994), Spanish adaptation was developed by Otero, Luengo, Romero, Gómez, and Castro (1998). The questionnaire consists of 10 items rated on a five-point Likert scale ranging from 1 (*totally disagree*) to 5 (*totally agree*). The dimension of Dispositional Optimism is evaluated with 6 items, the remaining 4 items are considered "fillers" and are intended to make the content of the test less evident. Of the 6 content items, 3 of them are worded positively (direction of optimism [O]) and 3 negatively (direction of pessimism [P]). Internal consistency of the scale in this sample was .80. High score indicates high dispositional optimism.

Happiness was evaluated with the Happiness Scale (Alarcón, 2006). This scale consists of 27 items rated on a five-point Likert scale. Items are classified into 4 subscales identified as Positive Sense of Life, Satisfaction with Life, Personal Realization, and Happiness of Living. The internal consistency coefficients of the subscales ranged from .80 to .87. Higher scores in each subscale indicate high happiness.

Results

Descriptive analyses were carried out to evaluate the means and standard deviations of the sample. Pearson correlation was conducted

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to assess relationships between variables. All analyses were carried out using the statistical software SPSS version 26.

Results showed (see Table 1) that scores in psychological well-being, optimism and affect (both negative and positive) were moderate however, participants scored high in all the Happiness subscales.

Table 1. Psychological wellbeing, optimism, affect and happiness variables

	Mean	DT	Min.-Max.
Psychological Wellbeing	179.40	27.62	79-229
Optimism	15.89	4.53	0-24
Positive Affect	27.63	6.04	14-41
Negative Affect	21.77	5.25	9-36
Happiness: Positive sense of life	49.47	6.91	11-55
Happiness: Satisfaction with Life	22.62	4.50	6-30
Happiness: Personal fulfillment	21.98	4.46	6-30
Happiness: Joy of Living	16.75	2.90	4-20

Regarding relationships between variables, shown in Table 2, Optimism had strong positive relationships with psychological well-being and all three Happiness subscales.

Table 2. Correlations between variables

	PW	DO	PA	NA	H_1-SPL	H_2-SL	H_3-PR
PW	1						
DO	.50***	1					
PA	.17	.04	1				
NA	.063	-.005	.841	1			
H_1-SPL	.74***	.47***	.007	-.05	1		
H_2-SL	.72***	,51***	.18	.12	.66***	1	
H_3-PR	.69***	.41***	.13	.05	.60***	.83***	1
H_4-HL	.65***	.50***	.23*	.17	.59***	.68***	.61***

PW: Psychological Wellbeing; DO: Dispositional Optimism; PA: Positive Affect; NA: Negative Affect; H_1-SPL: Positive sense of life; H_2-SL: Satisfaction with Life; H_3-PF: Personal realization; H_4-JL: Happiness of Living. $^{*}P<.05$; $^{***}P=.000$

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STUDY 2

Method

Procedure and Participants

A snowball sampling technique was used to gather data through digital internet questionnaires. Questionnaires were sent by email, Facebook, or Whatsapp, asking people to fill them in and also to send them to their relatives or friends to be filled in. Finally, 442 individuals completed all the questionnaires. Of this sample, 296 people performed regular physical exercise, so the final sample of this study was composed of 296 people (63.9% women), with a mean age of 35.13 years (*SD* = 13.63), and 61.8% were single.

Variables and Instruments

To assess optimism, resilience, self-esteem, and psychological well-being variables the following questionnaires were used:

Optimism and Psychological well-being were measured with the same instruments as in Study 1.

Resilience was measured with Brief Resilience Scale-BRS, developed by Smith et al. (2008). This study used the Spanish version carried out by Rodríguez-Rey et al., 2016. This scale measures people's resilience to stress. It consists of 6 items rated on a five-point Likert scale ranging from 1 (totally disagree) to 5 (totally agree). High scores indicate a high degree of resilience. In this sample, the internal consistency coefficient was .87. High scores indicate high resilience.

Self-esteem was assessed with *The Rosenberg Self-Esteem Scale (RSE).* This instrument was originally developed by Rosenberg (1965). The Spanish version and adaptation were carried out by Vázquez, García-Bóveda, and Vázquez-Morejón (2004). This scale consists of 10 items rated on a four-point Likert scale ranging from 1 (*strongly disagree*) to 4 (*strongly agree*). Five items are negatively worded and five are positively worded, obtaining a total score by adding all the items, and reversing the negative statements. The internal consistency coefficient in this sample was .85. High scores indicate high self-esteem.

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Results

As in Study 1, descriptive and correlation analyses were carried out.

As shown in Table 3, participants' scores in all the variables were between moderate and high. Moreover, all variables had positive and significant correlations with each other (see Table 4). The highest correlation was between Psychological Well-Being and Self-Esteem.

Table 3. Psychological wellbeing, optimism, resilience and self-esteem variables

	Mean	DT	Min.-Max.
Psychological Wellbeing	117.37	17.57	59-150
Optimism	22.13	4.47	8-30
Resilience	20.63	4.86	6-30
Self-esteem	42.57	6.51	16-50

Table 4. Correlations between variables

	Psychological wellbeing	Dispositional Optimism	Self-esteem
Psychological wellbeing	1		
Dispositional Optimism	.66***	1	
Self-esteem	.74***	.62***	1
Resilience	.54***	.56***	.53***

***P=.000

STUDY 3

Method

Procedure and Participants

A snowball sampling technique was used to gather data through digital internet questionnaires. Questionnaires were sent by email and Whatsapp, asking athletes to fill them in and also to send them to other athletes to be filled in. Finally, 181 athletes (defined as competitors in track and field events) completed all the questionnaires. Of them, 40

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practiced volleyball, 91 played football, and 40 competed in swimming, and 101 (55.8%) were men. Their mean age was 21.43 years (*SD* = 6.46), the mean number of years practicing sport was 11.21 years (*SD* = 4.70), and the mean number of hours of training per week was 8.28 (*SD* = 5.77).

Variables and Instruments

Emotional intelligence was assessed by the Schutte Self Report Inventory in athletes (SSRI; Schutte, 1998; Spanish adaptation by García et al., 2013). It is composed of 33 items rated on a five-point Likert scale ranging from 1 (*totally disagree*) to 5 (*totally agree*). It has four subscales (Emotional Perception, Self-Emotional Management, Hetero-Emotional Management, and Emotion Utilization). The internal consistency coefficients of the subscales ranged from .58 to .74. High scores indicate high emotional intelligence in each subscale.

Results

Descriptive analyses were conducted, and t-test analyses were performed to assess the differences between sports, emotional intelligence subscales, and gender.

Table 5. Emotional intelligence subscales according to different types of sport

Subscales	Type of sport	Mean	DT	Min-Max.
Emotional Perception	Volleyball	27.90	2.95	19-33
	Football	28.09	3.40	16-35
	Swimming	28.70	3.45	22-35
Self-emotional management	Volleyball	24.70	4.29	12-34
	Football	25.91	3.72	17-35
	Swimming	25.80	4.67	15-34
Hetero-emotional management	Volleyball	40.97	4.02	33-48
	Football	40.23	4.57	28-50
	Swimming	41.22	4.27	31-48
Emotion utilization	Volleyball	15.50	2.41	9-20
	Football	15.94	2.18	11-20
	Swimming	16.26	2.04	13-20

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Results indicated (see Table 5) that all the athletes in the study, regardless of the sport they played, obtained high scores in all the Emotional Intelligence subscales, but there were no differences between sports in each subscale. We found gender differences only in volleyball athletes. Males scored higher in Emotional Perception, $t = 3.06$, $p = .004$, Self-Emotional Management, $t = 2.49$, $p = .017$, and Emotion Utilization, $t = 2.43$, $p = .020$.

Discussion

The aim of this chapter was to analyze the relationships between some positive emotional and psychological variables in people who perform physical exercise or sport. Three studies were carried out to analyze positive emotions both in athletes and people from the general population who do regular exercise.

The first study, conducted with amateur athletes, revealed moderate scores in Optimism, Well-Being, and both Positive and Negative Affect, but the Happiness subscales showed high scores. On another hand, significant and positive correlations were found between Optimism, Well-Being, and the subscales of Happiness. However, Affect did not show any relationship with any of the variables evaluated. In this sense, our results do not agree with other works in which optimism correlates positively with positive affect, which was also the best predictor of satisfaction with life (Garcia Naveira, 2015). Nevertheless, preliminary studies have indicated that positive affect increases before sporting events and negative affect decreases after performing sports activity (Szabo et al., 2018). A possible explanation of the lack of a correlation between affect and other variables is that affect may be important before and after performing a sports activity, and not so much when the question is formulated at a general level, without performing an exercise. Given the results, optimism seems to play an important role in amateur athletes' well-being and happiness. It is essential to know the levels of optimism in sports because it also has a close relationship with sports performance (López-Gullón et al., 2017).

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The second study, conducted with an exercise-practicing population, found moderate scores in Well-Being and Resilience, whereas the scores in Self-Esteem and Optimism were high. Some studies have indicated that athletes with fewer years of experience in the sport have higher levels of optimism, and also that athletes with burnout symptomatology show less optimism and resilience (Tutte & Reche, 2016). Another study, also conducted with adolescents, found that self-esteem was positively related to athletic performance (Molina et al., 2017). Likewise, all the variables analyzed obtained positive and significant relationships with each other, which indicates a relationship between positive emotions and the practice of exercise. In our results, the highest correlations were found between Well-Being and Self-Esteem. Some studies indicate that high scores in resilience and optimism imply a greater ability to withstand training loads (Aranzana et al., 2017). Another study also confirmed a positive relationship between resilience and psychological well-being and athletic performance (Hosseini & Besharat, 2010). In short, this second study also confirmed that people who exercise have good psychological well-being, high optimism, resilience, and self-esteem.

Finally, in the third study, conducted with athletes who played three different sports (football, volleyball, and swimming). The results showed that the athletes scored high in all subscales of Emotional Intelligence, regardless of the sport they practiced. Thus, the results showed that emotions do not depend on the sport because the results in positive emotions were similar in athletes who played football, volleyball, and swimmers. Previous studies have found interactions between gender and the participation of athletes in teams, with males who had participated in team sports obtaining the highest score in emotional intelligence (León et al., 2018). Emotional intelligence is a variable that favors relationships with the coach and has been linked to wellness variables in sport (Martín de Benito et al., 2018). In our results, gender differences were only found in volleyball players, with males scoring higher in the subscales of Emotional Perception, Emotion Self-Management, and Emotional Utilization, which coincides with other works of emotional intelligence in sport (Castro-Sánchez et al., 2018).

No doubt, there are still many unanswered questions in research on positive emotions and their involvement in sports performance and

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achievement. Among the future challenges, we should consider whether competition makes athletes more emotionally attentive, or to analyze in detail the multiple direct relationships between positive emotions and their impact on athletes' well-being. In light of the data obtained, we recommend implementing psychological intervention programs focused on positive emotion management and specifically adapted to the population with which they work.

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Chapter 2

PHYSICAL ACTIVITY AS A COMPLEMENTARY AND ALTERNATIVE THERAPY FOR FIBROMYALGIA

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ABSTRACT

Physical activity is usually associated with several benefits for the individual's health, specifically in disease prevention. In the case of fibromyalgia, exercise emerged as one of the most

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indicated options to reduce signs and symptoms and seems to be useful in the management of this syndrome of unknown etiology. Knowing the importance of physical activity, it seems necessary to understand in-depth the quantity (e.g., volume, frequency), intensity (e.g., % of maximal load), and type of exercise (e.g., cardiorespiratory, resistance) that should be performed by an individual diagnosed with fibromyalgia. Therefore, this chapter aimed to critically analyze the literature on training programs that caused positive effects on the main symptoms of fibromyalgia and to suggest some practical applications regarding exercise program designs (i.e., type, volume, and intensity). A search was performed through Web of Science, Scopus, and Medline, and randomized clinical trials composed of individuals diagnosed with fibromyalgia who were over 18 years of age. Cardiorespiratory training, resistance training, and combined programs appear to be effective in reducing the symptoms associated with fibromyalgia. Aquatic exercises stand out in particular as they provide benefits generated by water along with the benefits of physical exercise. The frequency of two to three sessions per week with a progressive increase in intensity during the weeks of a training protocol seems to be effective, especially in medium to long term interventions.

Keywords: fibromyalgia, exercise, duration, intensity, training

INTRODUCTION

Recent data suggests that fibromyalgia affects about 0.2 to 6.6% of the global population (Marques et al., 2017). Fibromyalgia is defined as a neurological condition that causes sensory changes and muscle pain (Henriksson, 2009), although the physiopathology is not yet defined. Some studies suggest that fibromyalgia results from the imbalance of neurotransmitters and other hyperexcitability of the central nervous system (Schmidt-Wilcke & Clauw, 2011; Shipley, 2018). One of the main characteristics of fibromyalgia is the diversity of symptoms experienced by individuals affected by this syndrome since the clinical symptoms vary from individual to individual. Muscle pain, sleep disorders, depression, anxiety, fatigue, dizziness, headache, and nausea are some of the most reported symptoms (Busch, Webber et al., 2011; Wolfe, Ross, et al., 1995). It is known that the severity of

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symptoms negatively affects these individuals in a way that physically compromises exercising (Jones, Rutledge et al., 2008). As a result of this, female fibromyalgia patients have a lower capacity to perform physical activities compared to healthy women (Mannerkorpi, Burckhardt et al., 1994). These physical impairments can reduce active lifestyle habits and contribute to increases in sedentary behavior (Segura-Jiménez et al., 2015).

The recommended treatments to reduce the symptoms of fibromyalgia are usually pharmacological and/or non-pharmacological (Carville et al., 2008; Wolfe, Clauw et al., 2011). Specifically, exercise emerged as one of the most indicated options to reduce signs and symptoms of fibromyalgia and seems to be important in the management of this syndrome of unknown etiology (Hakkinen et al., 2001). Exercise is a low-cost activity that promotes physical and psychological benefits (Valim, Natour et al., 2013). Populations affected by fibromyalgia syndrome can find several benefits as previously described in the literature, such as a reduction in the number of tender points, reduction of pain, improvements in functional capacity, sleep, and quality of life (Acosta-Gallego et al., 2018; Moore et al., 2016). Aerobic exercise, resistance exercise, flexibility, and combined exercise are some of the exercise programs that have already shown positive results for this specific population (Andrade et al., 2017; Hakkinen et al., 2001; Jones, Burckhardt et al., 2002; Sanudo, Galiano, Carrasco, Blagojevic et al., 2010). In addition to the diversity of the type of exercise, other factors may arise as barriers when choosing a specific exercise for this population. It seems necessary to understand in-depth the quantity (e.g., volume, frequency), intensity (e.g., % of maximal load), and type of exercise (e.g., cardiorespiratory, resistance) that should be performed by an individual diagnosed with fibromyalgia. Therefore, the current chapter aims to critically review the literature regarding the training programs that cause positive effects on the main symptoms of fibromyalgia and to suggest practical applications regarding exercise variables (i.e., type, duration, volume, intensity).

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METHODS

Search Strategy

For this review of literature, a search in three different databases (Pubmed, Web of Science, and Scopus) was carried out. The keywords chosen for the search were: fibromyalgia, exercise, physical activity, strength, flexibility, aerobic exercise, resistance exercise, and randomized controlled trial. There were not any restrictions related to the research period, but the type of document and language was elected. Only articles written in English were included. The inclusion criteria comprised, i) randomized clinical trials; ii) the study population over the age of 18; iii) patients diagnosed with fibromyalgia syndrome following the criteria established by the American College of Rheumatology (ACR); iv) intervention protocol consisting of a minimum period of 6 weeks; v) aim to evaluate the effects of a protocol composed of physical exercise; vi) include assessment instruments that analyze at least one of the symptoms presented by typical fibromyalgia patients (eg, depression, sleep, anxiety) vii) present at least one intervention group and a control group (without any intervention). Reviews of literature, thesis, and dissertations, educational or cognitive-behavioral therapies were not included for analysis.

RESULTS

Different approaches to exercise were taken in their respective intervention protocols. Among them, the types of analyzed exercise were cardiorespiratory training, resistance, flexibility, and combined protocols (resistance and cardiorespiratory). Most of the research evaluated symptoms and the impact of fibromyalgia syndrome by applying the fibromyalgia impact questionnaire (FIQ), and the assessment of the quality of life, depression, anxiety, strength, and pain threshold.

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Overview of the Effects of Exercise in Fibromyalgia

The literature has long demonstrated the positive effects of physical exercise on an individual's health and physical fitness (Acosta-Gallego et al., 2018). More recently, it has been suggested to relieve symptoms caused by fibromyalgia as a complement in the treatment of this syndrome (Macfarlane et al., 2017; Moore et al., 2016). People with fibromyalgia tend to be sedentary and as such some physical and psychological symptoms may be more severe in this population. It is widely known that physical inactivity can promote the development of several health problems, and reduce the quality of life (Ellingson et al., 2014). Approximately 20 minutes of exercise per day can already promote some health benefits (Pescatello et al., 2014), and this is clear in individuals with fibromyalgia. Gavilán-Carrera et al. (2019) showed that replacing 30 minutes of physical inactivity for physical activity can be extremely effective in reducing symptoms of fibromyalgia such as body pain, vitality, social function, and disease impact. The reduction of body pain can be justified by the important association of physical activity with a better capacity for pain regulation and pain perception (McLoughlin et al., 2011).

Regardless of the type of physical activity to be performed (cardiorespiratory training, resistance, flexibility or combined), it is possible to perceive the improvement of at least one of the reported symptoms. Several physical benefits were found in the literature, such as reduction of pain (Andrade, Zamuner, Forti, Tamburus et al., 2018; Hakkinen et al., 2001; Kayo et al., 2012; Letieri et al., 2013; Roman et al., 2015), number of tender points (Roman et al., 2015), pressure pain threshold (Andrade, Zamuner, Forti, Tamburus et al., 2018; Munguia-Izquierdo & Legaz-Arrese, 2008; Roman et al., 2015), disability level (Nichols & Glenn, 1994), impact of the disease (Andrade, Zamuner, Forti, Tamburus et al., 2018; Assumpção et al., 2018; Gowans et al., 2001; Kayo et al., 2012; Roman et al., 2015; Sanudo, Galiano, Carrasco, de Hoyo et al., 2011; Tomas-Carus et al., 2008), functional capacity gains (Tomas-Carus et al., 2008), aerobic capacity (Andrade, Zamuner, Forti, Tamburus et al., 2018; Valkeinen et al., 2008), muscle strength (Hakkinen et al., 2001; Mengshoel et al., 1992; Roman et al., 2015; Valkeinen et al., 2008), variability of heart rate (Sanudo,

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Carrasco, de Hoyo, Figueroa et al., 2015), balance (Roman et al., 2015), sleep quality (Munguia-Izquierdo & Legaz-Arrese, 2008), physical fitness (Munguia-Izquierdo & Legaz-Arrese, 2008), and physical function (Gowans et al., 2001). In addition to physical benefits, there was also an emphasis on psychosocial gains, namely anxiety (Gowans et al., 2001; Sanudo, Carrasco, de Hoyo, Figueroa et al., 2015; Tomas-Carus et al., 2008), quality of life (Assumpção et al., 2018; Kayo et al., 2012; Letieri et al., 2013; Sanudo, Galiano, Carrasco, de Hoyo et al., 2011), psychological profile (Nichols & Glenn, 1994), cognitive function (Munguia-Izquierdo & Legaz-Arrese, 2008), depression (Gowans et al., 2001; Hakkinen et al., 2001; Letieri et al., 2013), auto-efficacy (Gowans et al., 2001), general mental health (Gowans et al., 2001), and well-being (Andrade, Zamuner, Forti, Tamburus et al., 2018). These benefits may take between 8 to 10 weeks to occur after the beginning of the program, although, in some cases, pain reduction can be found at the beginning of the process (Valim, Oliveira et al. 2003).

In order to obtain specific benefits from physical activity, it is essential to know and define other parameters such as training period, session duration, frequency of practice, and intensity of the exercises to be performed. The exercise programs focused on patients diagnosed with fibromyalgia ranged between eight weeks and eight months. A medium period (16 to 20 weeks) of intervention seems to present better results in a large number of symptoms. It is important to report that most of those were performed in the aquatic context, highlighting the benefits of aquatic exercise for this population. The specific aquatic context might increase muscle relaxation and improve blood flow, improving the well-being of these populations (Altan et al., 2004; Jentoft et al., 2001). Moreover, two or three sessions per week with a duration between 30 to 60 minutes seem to be the most recommended practices. The exercise should start with low intensity and be gradually increased over the weeks, as a response to the developed comfort of the participant in performing the exercise.

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The Specific Effect of Cardiorespiratory Training

Cardiorespiratory training has been widely recommended for the population with fibromyalgia (Mannerkorpi, Nyberg et al., 2000; Steffens et al., 2011) with a duration of 30 to 45 minutes (Andrade, Zamuner, Forti, Tamburus et al., 2018; Gowans et al., 2001). Nevertheless, there is evidence that a shorter duration per session can be effective as well, due to the usual low level of physical fitness and consequent low tolerance to exercise presented by individuals with fibromyalgia. This could become a limiting factor for longer practices (Norregaard et al., 1997). Improvements were found in 30 minutes of aerobic exercise, specifically in the quality of life (Gowans et al., 2001). Performing exercises at high intensities and durations can lead to quitting and become a barrier to the practice of physical exercise (Steffens et al., 2011).

The cardiorespiratory training programs demonstrated positive effects in pressure pain threshold (Andrade, Zamuner, Forti, Tamburus et al., 2018), pain (Andrade, Zamuner, Forti, Tamburus et al., 2018; Kayo et al., 2012) disease impact (Andrade, Zamuner, Forti, Tamburus et al., 2018; Gowans et al., 2001; Kayo et al., 2012), well-being (Andrade, Zamuner, Forti, Tamburus et al., 2018), aerobic capacity (Andrade, Zamuner, Forti, Tamburus et al., 2018), depression (Gowans et al., 2001), anxiety (Gowans et al., 2001; Sanudo, Carrasco, de Hoyo, Figueroa et al., 2015), physical function (Gowans et al., 2001), mental health (Gowans et al., 2001), auto-efficacy (Gowans et al., 2001), the variability of heart rate (Sanudo, Carrasco, de Hoyo, Figueroa et al., 2015), quality of life (Kayo et al., 2012), psychological profile (Nichols & Glenn, 1994), and incapacity level (Nichols & Glenn, 1994). Those cardiorespiratory programs that accumulated benefits in more parameters were those that were carried out in the aquatic environment (Andrade, Zamuner, Forti, Tamburus et al., 2018; Gowans et al., 2001).

The cardiorespiratory programs should be performed two or three times per week, for a minimum period of four to six weeks (Häuser et al. (2010). It can be noted that the performed exercises with shorter sessions in an aquatic environment, either in whole or in part (water and land) are effective when reaching a greater number of improved

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parameters related to fibromyalgia syndrome. As supported by Clark (1994) for better tolerance of aerobic exercise in this population, there must be a reduction in the time of the session and an increase in the frequency of these exercises. This way, the individual will be able to perform the exercises without reaching high levels of fatigue, remaining active due to the increased frequency. Regarding the exercise intensity, the American College of Sports Medicine (Pescatello et al., 2014) suggests starting at intensities ≤ 60% of heart rate reserve and gradually increase it, according to the individual adaptation to exercise.

The Specific Effect of Resistance Training

Another type of physical exercise that also brings benefits to this specific population is resistance training, especially for those with physical impairments (Bjersing et al., 2017). Although there are few investigations on the effects of resistance exercise in fibromyalgia symptoms, some investigation reports benefits for muscle strength (Hakkinen et al., 2001; Roman et al., 2015), cervical pain (Hakkinen et al., 2001), depression (Hakkinen et al., 2001), disease impact (Assumpção et al., 2018; Kayo et al., 2012; Roman et al., 2015), quality of life (Assumpção et al., 2018; Kayo et al., 2012), balance (Roman et al., 2015), pressure pain threshold (Roman et al., 2015), the number of tender points (Roman et al., 2015) and pain (Kayo et al., 2012; Roman et al., 2015).

Hakkinen et al. (2001) demonstrated that a well-structured resistance program with progressive changes in intensity resulted in significant gains of muscle strength. These authors showed that physical inactivity is harmful to individuals with fibromyalgia and that resistance training is beneficial to reduce negative neuromuscular symptoms. Besides improving the patient’s strength, it seems that resistance training contributed to the reduction of the number of tender points and increased balance when compared with other training types (Roman et al., 2015). It is important to highlight that resistance training can also reduce fatigue during daily activities (Ericsson et al., 2016), lessen pain disabilities, increase pains acceptance (Larsson et al., 2015), decrease anxiety (Andrade, Sieczkowska et al., 2019), and enhance sleep quality (Bircan et al., 2008).

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Regarding the resistance training intensity, one of the most common ways of determining the intensity is the percentage of one-repetition maximum (1-RM), even for the population with fibromyalgia. It is suggested that the intensity of the exercises aimed at this population should vary between 50%-80% 1-RM. (Pescatello et al., 2014). Despite these guidelines, Assumpção et al. (2018) argue that the use of this test to determine the intensity can generate an overload on the patient as well as trigger negative symptomatology. To determine the intensity, they decided to use the subjective Borg perceived exertion scale. This scale presents a variation in which the individual determines if the exercise intensity is: "No exertion at all", "Extremely light", "Very light", "Light", "Somewhat hard", "Hard (heavy)","Very hard", "Extremely hard", "Maximal exertion" (Pescatello et al., 2014). The classification from "Somewhat hard" to "Very hard" is enough to improve muscular fitness in healthy individuals (Lagally & Amorose, 2007). Besides being used with healthy individuals in resistance training, the subjective Borg scale can help preventing the risk of fatigue in patients with fibromyalgia. Progressing the intensity of exercise during a training protocol can help to prevent fatigue. Increasing the exercise intensity gradually during a training protocol also helps to reduce the symptoms (Assumpção et al. 2018). This gradual evolution is effective in benefiting the symptomatology of this population (Larsson et al., 2015; Valkeinen et al., 2008). The lack of a well-designed training program can negatively affect the results, in addition to having consequences for participants and dropouts throughout the study (Norregaard et al., 1997). Although these benefits are demonstrated statistically after the training period, it is essential to keep the practice of exercise a habit, otherwise, there may be a reduction of these benefits returning to a baseline value found at the beginning of the intervention (Larsson et al., 2015).

Effects of Combined Training

Combined training exercises are the most common type of studied exercise (Jones, Burckhardt et al., 2002). Most of the studies combined cardiorespiratory training with resistance training. Likewise some of the

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cardiorespiratory programs mentioned above, many investigations were carried out in an aquatic environment. Considering the benefits of this practice in the combined exercise modality, several studies reported clear progresses in dry-land and aquatic training (Letieri et al., 2013; Munguia-Izquierdo & Legaz-Arrese, 2007, 2008; Tomas-Carus et al., 2008). Combined training usually takes a longer time to be completed, as it includes two different exercise types during the same session. In this way, most research present benefits with a training duration between 45 to 90 minutes, two or three times per week (Munguia-Izquierdo & Legaz-Arrese, 2008; Sanudo, Galiano, Carrasco, de Hoyo et al., 2011; Valkeinen et al., 2008). The benefits found by these studies were: improved pressure pain threshold and sleep (Munguia-Izquierdo & Legaz-Arrese, 2008), cognitive improvement (Munguia-Izquierdo & Legaz-Arrese, 2008), improved physical fitness (Munguia-Izquierdo & Legaz-Arrese, 2008), reduced impact of illness (Sanudo, Galiano, Carrasco, de Hoyo et al., 2011; Tomas-Carus et al., 2008), lowered anxiety (Tomas-Carus et al., 2008), increased aerobic capacity (Valkeinen et al., 2008) and muscle strength (Valkeinen et al., 2008), enhanced quality of life (Letieri et al., 2013; Sanudo, Galiano, Carrasco, de Hoyo et al., 2011), decreased depression (Letieri et al., 2013) and pain (Letieri et al., 2013).

It was expected that combined training would result in great positive changes, because of the stimuli from multiple exercise types. However, the complexity of the combination of two training types and the longer duration needed for each session most likely interfered with the outcomes. Among the combined interventions, the study by Valkeinen et al. (2008) presented one of the biggest variations in session time (60-90 minutes). Despite this, the study found benefits in terms of aerobic capacity and muscle strength after the training protocol, a factor that demonstrates the ability to obtain benefits in long training sessions with this population. In this type of training, given the different stimuli assigned to the individuals from aerobic and strength training, professionals must be aware of the possible exacerbations of symptoms during the performance of the exercises. For instance, the use of a scale for assessing pain and fatigue can be used to reduce such risks (Pescatello et al., 2014).

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Effects of Balance and Flexibility

Balance and flexibility are topics less investigated regarding individuals with fibromyalgia (Demir-Gocmen et al., 2013). Consequently, it is difficult to find enough evidence regarding the effects of a specific protocol focused on these two parameters (Busch, Schachter et al., 2008). Despite this gap in the literature, some studies showed that individuals with fibromyalgia have balance disorders that compromise their daily activities (Jones, Horak et al., 2009). Balance disorders are more common than perceived. In a survey applied by Bennett et al. (2007) to 2,596 individuals diagnosed with fibromyalgia, 45% had disturbances in balance, with percentage values higher than anxiety and depression, symptoms relatively common to this population. As an intervention method to improve the balance of individuals with fibromyalgia, the most common is the use of a vibrating platform (Gusi et al., 2010; Sanudo, Carrasco, de Hoyo, Oliva-Pascual-Vaca et al., 2013; Sanudo, de Hoyo et al., 2012). However, benefits can also be found through the use of protocols with other balance exercises. These benefits included reduction of pain severity, improvement in exercise capacity and quality of life (Duruturk et al., 2015). In our point of view, approaches that aim to improve individual balance skills may be included when designing resistance and/or cardiorespiratory training programs. Consequently, the individual can also benefit from one more aspect that usually affects this population (Demir-Gocmen et al., 2013).

According to Jones, Horak et al. (2009), a reduction in flexibility in conjunction with other factors can affect body balance. This relationship can be justified by the fact that lack of flexibility can compromise the range of motion of the joints and affect the ability to restore balance in the face of an external force (Chiacchiero et al., 2010). The physiological characteristics evidenced in aging can be related to the consequences generated by the symptoms of fibromyalgia since these individuals also suffer a loss of strength and flexibility due to physical inactivity. As a result, balance control can become impaired. Because the population with fibromyalgia has in large majority a sedentary behavior, performing any type of minimal activity or movement independently of its type can bring benefits to this population (Jones,

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Burckhardt et al., 2002). Although there is not enough evidence in the literature for the benefits of flexibility, in one survey with 2.596 diagnosed individuals, 62% prioritized this practice over aerobic exercises (32%) and strength exercises (18%) (Bennett et al., 2007). Some articles that evaluate the effects of a stretching protocol find benefits such as reducing pain and sensitivity of tension points, improving quality of life (Matsutani et al., 2007), sleep, and morning stiffness (Bressan et al., 2008). When compared to other types of exercise, stretching protocols have fewer benefits, nevertheless this type of intervention should not be considered as a placebo (Valim, Oliveira et al., 2003). Furthermore, the use of flexibility exercises in warming up and/or cool-down are frequent in several studies, a factor that is not generally considered in the results (Kim et al., 2019).

CONCLUSION

Physical activity is essential to help reduce the symptoms presented by the population diagnosed with fibromyalgia. To summarize our critical review, we should conclude that:

- Programs with an intermediate duration of 16 to 20 weeks and long-term programmes are more effective in reducing a greater number of symptoms when compared to short-term interventions, although these interventions are also beneficial.
- A frequency of two to three sessions per week seems to positively affect the patients, but specific attention regarding the intensity of the exercises is necessary.
- A short to moderate training time (30-60 minutes) is preferably suggested, always considering the intensity of the performed exercises to avoid the individual’s fatigue.
- Cardiorespiratory programs are effective in reducing symptoms and seem to be more efficient when performed in aquatic environments.
- The intensity of cardiorespiratory training should be implemented starting between 40-50% maximal heart rates and

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be gradually increased during the following weeks up to maximum values of 80% of maximal heart rates.

- Resistance training should be performed to achieve better results.
- When structuring and planning an intervention plan for the individual with fibromyalgia, the intensity of the exercises should be performed starting with low loads (40-50% of 1RM) and gradually increasing these values until reaching the final aimed intensity.
- Exercise protocols that provide positive effects to as many symptoms as possible should be prioritized, namely, more global effects should be selected.
- Individualization at the time of the intervention is crucial, considering the needs of each person and adjusting when necessary.

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Chapter 3

CAN PHYSICAL ACTIVITY REGULATE INSULIN RESISTANCE?

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ABSTRACT

Insulin resistance (IR) is a condition that occurs when muscle, fat, and liver cells do not respond well to insulin and cannot easily absorb glucose from the blood. Muscles play a very important role in insulin resistance because they are the main glucose storage site in the human body as well as an important regulator of blood glucose levels, both in acute reactions and by means of chronic adaptations through physical training. Our aim is to review the molecular mechanisms of insulin action and the causes of insulin resistance as well as discuss the data available on the effects of physical activity on insulin resistance.

Regarding the different types of physical activity, resistance training produces better adaptations for the restoration of metabolic flexibility in subjects with insulin resistance. These adaptations include an increase in the expression of insulin receptor protein; an increase in AMPK activity, which leads to an increase in ATP production in fatty acid oxidation and glucose absorption processes; the stimulation of muscle glycogen synthesis; and protection from mitochondrial dysfunction.

Resistance training has been shown to improve insulin action measured in skeletal muscle. This type of training reduces the percentage of glycosylated hemoglobin, increases glucose elimination, and improves metabolic and lipid profiles. In addition, it increases the expression of GLUT4 protein content, which is essential for transmembrane translocation in the skeletal muscle, facilitating the action of insulin in carbohydrate metabolism in normal skeletal muscle. Furthermore, it is able to reverse insulin resistance induced by a high-fat diet by altering the activity of key components in insulin signaling.

The analyzed literature suggests that resistance training (RT), regardless of the intensity at which it is performed, produces important improvements in insulin sensitivity and body composition and that the longer the duration of the RT protocol, the greater these improvements are. Therefore, RT should be a mainstay in the management of IR in people with overweight or obesity and should always be included as a central, fundamental intervention in any training program, regardless of its intensity.

Keywords: insulin resistance, physical activity, resistance training, muscle strength, insulin sensitivity

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1. INSULIN RESISTANCE AND METABOLIC SYNDROME

Metabolic syndrome (MS) describes a set of risk factors that includes abdominal obesity, insulin resistance (IR), hypertension, and dyslipidemia. It predisposes individuals to many metabolic and cardiovascular disorders (Cornier et al., 2008) such as diabetes mellitus (Ford et al., 2008), non-alcoholic fatty liver disease (Kim et al. 2018), chronic kidney disease (Chen, et al. 2004), and polycystic ovary syndrome (Ali, 2015). MS and its comorbidities are associated with premature mortality and represent a public health problem worldwide (Cornier et al., 2008).

MS is also known as “insulin resistance syndrome,” as a substantial part of the pathophysiology is driven by resistance to the metabolic effects of insulin. Therefore, IR is believed to be at the core of most cases of MS (Samson & Garber, 2014; Ighbariya & Weiss, 2017). According to Ighbariya and Weiss (2017), “Insulin resistance is a condition that occurs when muscle, fat, and liver cells do not respond well to insulin and cannot absorb glucose from the blood easily. As a result, the pancreas produces more insulin to help glucose enter the cells”. However, the pancreas will not always be able to produce enough insulin to overcome the cells’ weak response to insulin. This causes blood sugar levels to rise excessively, outside of a healthy range (Ighbariya & Weiss, 2017). This state, in which blood sugar levels are elevated above the normal range, is known as prediabetes, as the levels are not high enough for a diagnosis of diabetes to be made.

Prediabetes occurs primarily in people with some IR or people whose pancreatic β-cells are not producing enough insulin to maintain basal levels (Ighbariya & Weiss, 2017). If this situation persists over time and there is not enough insulin available, the extra glucose will remain in the blood instead of entering the cells and the risk of developing type 2 diabetes mellitus (T2DM) will increase exponentially (Golay & Ybarra, 2005).

The ability to maintain normal blood glucose levels involves a complex interaction between insulin secretion by pancreatic β-cells and metabolic responsiveness to insulin in the skeletal muscle, liver, adipose, and other tissues. Insulin is a potent anabolic hormone.

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Binding to its receptor activates downstream intracellular signaling pathways that regulate nutrient metabolism, fluid homeostasis, growth, ion transport, maintenance of vascular tone, and other functions. Insulin also acts by binding to receptors on the membrane of target cells, inducing the uptake of glucose in skeletal muscle and adipose tissues. In the liver, it decreases glucose production and output (Avruch, 1998). The interaction of insulin with its receptor induces a conformational change and autophosphorylation, leading to the recruitment and phosphorylation of receptor substrates such as insulin receptor substrate and Shc proteins. The latter activates the Ras/mitogen-activated protein kinase (MAPK) pathway whereas insulin receptor substrate proteins mostly activate the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway by recruiting and activating PI3K. The Ras/MAPK pathway, together with the PI3K pathway, is key in the regulation of gene expression and the control of cell growth and differentiation, which are vitally important in the vast majority of the metabolic effects of insulin (Boucher at al., 2019; Russo et al., 2019).

Insulin signaling also plays a critical role in activating nitric oxide synthase, which regulates nitric oxide production (Steinberg et al., 1994; Zeng et al., 2000; Montagnani et al., 2001). Defects in insulin signaling can produce both a decrease in glucose utilization and a decrease in the degree of activation of the enzyme nitric oxide synthase, producing nitric oxide deficits. This can lead to hypertension and accelerated atherosclerosis in the body due to the powerful vasodilating and antiatherogenic effect that nitric oxide produces in the body (Brunner et al., 2005). IR causes the activation of multiple inflammatory pathways due to the chain of Pl3-kinases with intact MAPK signaling. Two of the most important inflammatory pathways are the inhibitor kB (lkB)/nuclear factor kB (NFkB) and the c-jun N-terminal kinase (JNK) pathways, which favor a prediabetic state in the individual (Wang et al., 2004). Physiological hyperinsulinemia is responsible for the activation of a large number of genes related to tissue inflammation (Hirosumi, J. at al., 2002).

IR also has very important effects in other areas, such as in skeletal muscle, which is responsible for more than 75% of all insulin-mediated glucose disposals (Wei et al., 2008). In skeletal muscle, insulin binds to

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the insulin receptor on the sarcolemma, increases insulin receptor tyrosine kinase activity, and phosphorylates insulin receptor substrates (IRS-1, IRS-2). Tyrosine phosphorylation of IRS-1 results in engagement of the p85 regulatory subunit of PI3K and activates the p110 catalytic subunit, which increases phosphoinositides. This leads to activation of phosphoinositide-dependent protein kinase and downstream protein kinase B (PKB; Akt) and/or atypical protein kinase C (PKC; Ishiki & Klip, 2005). Phosphorylation of Akt substrate of 160 kDa (AS160), which has a GTPase-activating domain (Rab4), facilitates translocation of GLUT4 to the sarcolemma to facilitate glucose entry into the cell. Intracellular glucose is then rapidly phosphorylated by hexokinase and directed to oxidative or non-oxidative pathways, which is known as glycogen synthesis (Sakamoto & Holman, 2008). The AS160 protein seems to act as a common point in both the insulin and muscle contraction metabolic pathways in order to facilitate translocation of GLUT4 (Kramer et al., 2006).

IR is categorized into three types: pre-receptor, receptor, and post-receptor. Categorization is based on where the pathology is located (Hari Kumar, 2020). IR is characterized by an altered cellular response to physiological levels of insulin. It impairs the phosphorylation signaling pathway of the skeletal muscle and adipose tissue, leading to decreased GLUT4 expression and translocation, resulting in impaired glucose uptake. In the liver, it promotes gluconeogenesis and suppresses glycogen synthesis (Guo, 2014).

The two key organs that help maintain glucose homeostasis and a proper response to insulin are the skeletal muscle and the liver. It is therefore important to understand the cellular mechanisms that cause these organs to become resistant to insulin (Lowell & Shullman, 2005). In order to understand the effect of physical exercise on IR and MS, we need to understand why IR occurs and what the main mechanisms involved are. IR is associated with a series of metabolic and cardiovascular disorders (dyslipidemia, hypertension, visceral obesity, glucose intolerance, endothelial dysfunction), which are independent risk factors for cardiovascular disease (CVD).

The molecular underpinnings of alterations in insulin-stimulated glucose metabolism involve two events: insulin signaling alterations

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caused by phosphoinositide-3 kinase pathway activation and intact signaling through the mitogen-activated protein kinase pathway.

T2DM and obesity are characterized by low-grade chronic inflammation, which could contribute to accelerated atherosclerosis (Evans et al., 2002; Garg et al., 2003). Increased ıkb/NFkb (Nuclear factor kappa-light-chain-enhancer of activated B cells) activity is a molecular mechanism responsible for inflammation and IR in T2DM (Duckworth, W. et al. 2009). The free NFkB translocates to the nucleus, where it binds to target genes, stimulating the inflammatory mediators (TNFa, IL-1B, IL-6, PKC) involved in atherogenesis (Evans et al., 2002; Barnes et al., 1997; Yamamoto et al., 2004). These cytokines also cause serine phosphorylation of IRS-1, inhibiting insulin signaling and causing IR (De Alvaro et al., 2004). Furthermore, adipocytes also produce adiponectin, a potent insulin-sensitizing, antiatherogenic cytokine. All these mechanisms lead to a state called lipotoxicity (Wende et al., 2012). Lipotoxicity is the deleterious effect of the accumulation of fatty tissue on glucose metabolism (Yazıcı & Sezer, 2017). Nonessential fatty acid (NEFA) elevation in T2DM causes severe muscle/liver IR and inhibits insulin secretion (Yazıcı & Sezer, 2017). Intramyocellular and intrahepatic fat accumulation are closely associated with organ-specific IR. Intracellular toxic metabolites of triacylglycerol (TAG) and NEFA metabolism [long-chain fatty acyl COAs (LCFA-CoA), diacylglycerol, ceramides] cause severe IR by impairing insulin signaling and multiple intracellular steps of glucose metabolism (Kashyap et al., 2004; Belfort et al., 2005). Elevated plasma NEFA impairs glucose oxidation/glycogen synthesis and decreases glucose transport/phosphorylation (Kashyap et al., 2004). What’s more, the greater the amount of adipose tissue in the body, the greater the degree of macrophage infiltration in this tissue will be. Increases in adipose tissue cause a change in the polarization of these macrophages, which go from having an M2 profile (anti-inflammatory secretor) to an M1 profile (proinflammatory secretor; Weisberg et al., 2003).

Mitochondria also seem to play a central role in the development of IR (Ruegsegger et al., 2018). IR in skeletal muscle is related to increased mitochondrial oxidative production in response to excess “fuel” compared to demand, leading to decreased insulin signaling and

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glucose transport in skeletal muscle (Rindler et al., 2013). As a result of mitochondria dysfunction, a decrease in mitochondrial fatty acids leads to higher levels of intracellular acyl-CoA and diacylglycerol, which interfere with insulin signaling (Lowell et al., 2005). Skeletal muscle mitochondria in individuals with T2DM show decreased respiratory chain activity (Kelley et al., 2002). Peluso et al. (2002) analyzed skeletal muscle from subjects with IR and found that mitochondrial carnitine acylcarnitine was especially decreased relative to subjects without IR, suggesting that this decrease could contribute to high muscle concentrations of triglycerides, diacylglycerol, and fatty acid-coenzyme A, a key characteristic of muscle with IR (Peluso et al., 2002)). To sum up, there are two key mechanisms in mitochondrial function that explain IR in skeletal muscle: a) a decrease in the oxidation of mitochondrial fatty acids due to mitochondrial dysfunction, and b) an increase in the oxidative production of the mitochondria in response to excess glucose (Di Meo et al., 2017). In fact, according to Houstis et al., (2006), "the increased production of reactive oxygen species (ROS) is an early indicator of the development of IR" (Houstis et al., 2006).

MS is strongly linked to excess calorie consumption, excess adipose tissue, physical inactivity, and genetic factors. Thus, the mainstay of treatment for MS and, in particular, for IR, continues to be lifestyle changes with physical activity and diet to induce weight loss (Lee et al., 2015), which is linked to lower grades of inflammation and oxidative stress.

2. Metabolic Pathways: Can Physical Activity Modify Insulin Resistance Status?

"Regular physical activity produces healthy effects, including increased tissue metabolism, due to mitochondrial proliferation," state Venditti et al., (2016; Venditti et al., 2016). Physical activity produces an increase in the number of myofibrils which in turn produces an increase in the cross-sectional area of the muscle. This muscle expansion causes an important increase in resting metabolism, with substantial benefits for individuals' health (Di Meo et al., 2017).

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Physical activity has a very positive impact on the individual through various mechanisms and factors. Indirectly, it improves insulin sensitivity, as an increase in resting metabolism and regular physical activity will produce greater caloric expenditure, helping the body to lose fat and improve muscle health (Di Meo et al., 2017). The results of numerous studies have shown that regular physical activity reduces the risk of several illnesses, including cardiovascular diseases, T2DM, some types of cancer, osteoporosis, fall-related injuries, depression, and obesity (Simoni et al., 2018).

Directly, physical activity can produce multiple health benefits for an individual suffering from MS. One of the most important benefits is an increase in the number and efficiency of mitochondria in skeletal muscle cells, producing greater oxidation and energy production both at rest and during activity. As we have mentioned, improvements in the respiratory chain lead to a substantial decrease in the risk of developing T2DM (Di Meo et al., 2017).

As stated above, increased production of ROS is an early indicator of the development of IR. Indeed, a single session of strenuous or prolonged exercise leads to the production of high amounts of radicals and other ROS, which cause tissue damage and dysfunction (Di Meo et al., 2019). How then is it possible that physical exercise can produce health benefits and improve mitochondrial efficiency by reducing the risk of T2DM? It is possible because of the double role, depending on the extent of their production, played by oxidants in living systems. If produced to a massive extent, oxidants cause oxidative damage and tissue dysfunction. On the other hand, when produced in moderation, they serve as molecular signals that activate adaptive responses that are useful for the organism (Di Meo et al., 2019).

The balance of free radicals inside the skeletal muscle is very important, particularly in the context of exercise and sport, as the main adaptations occur in trained skeletal muscle. Adaptations may differ according to the type of exercise, but nevertheless seem to be dependent on ROS production. Aerobic physical activity induces skeletal muscle adaptive responses that are able to increase resistance to the conditions in which ROS production increases, including prolonged or strenuous exercise (Di Meo et al., 2019). Conversely, heavy resistance exercise induces hypertrophy and increased strength

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production, but does not change the biochemical characteristics of muscle cells. Metabolism of glucose and lipids in skeletal muscles during rest and insulin action in insulin-resistant individuals are improved in skeletal muscle by both aerobic and resistance training, leading to decreased rates of progression to overt diabetes (Colberg, 2007).

A systematic review by Umpierre et al., (2011) found that individuals who exercised for a minimum of 150 minute per week showed a significant reduction in HbA1c (0.89%) compared to those who exercised less than 150 minutes (Umpierre et al., 2011). Another systematic review and meta-analysis investigating the effect of short-term exercise training (less than two weeks) on glycemic control, as measured by continuous glucose monitoring in adults with T2DM, showed that exercise significantly reduced hyperglycemia (>10.0 mmol/L), but did not significantly change fasting blood sugar (FBS) levels (Way et al., 2016).

2.1. Aerobic Exercise

Aerobic exercise (AE) decreases the prevalence of cardiovascular and metabolic risk factors and improves body composition, the waist-hip ratio, HDL and LDL cholesterol levels, respiratory capacity, and fasting blood glucose (FBG) levels (Wewege et al., 2018). AE enhances muscles' aerobic metabolism capacity, but does not induce increases in muscle mass or the development of strength. Indeed, in skeletal muscle, endurance training transforms the muscle fiber type, increases mitochondrial mass, and produces new blood vessels and other adaptations (Yan et al., 2011). An increase in muscle blood vessels is a necessary adaptation to an increased demand for mitochondrial oxygen (Prior et al., 2004). The increase in the mitochondrial compartment is accompanied by an increase in the enzyme content of both the Krebs cycle and oxidative phosphorylation, including succinate dehydrogenase (SDH), citrate synthase (CS), and cytochrome c oxidase (COX; Reichmann et al., 1985). As a result of these adaptations and of increased capillarization, oxidative capacity is greatly enhanced in endurance-trained muscle. The adaptations

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elicited by endurance exercise boost resistance to exercise performed at an intensity that, in an untrained state, can only be performed for shorter period of time.

Dela et al., (2004) showed that three months of AE improved β-cell function in individuals with T2DM (Dela et al., 2004). Another study showed that a 12-week AE intervention improved β-cell function in older adults with obesity and individuals with T2DM (Kirwan et al., 1993). O'Donovan et al., (2005), Lazarevic et al., (2006), and Mavros et al., (2013) found a significant difference in body mass index (BMI) after AE interventions when compared to control groups (O'Donovan et al., 2005; Lazarevic et al., 2006; Mavros, et al., 2013) whereas in two other studies by Short et al. (2003), no significant differences were found between the intervention and control groups (Short et al., 2003). A recent review of individuals with T2DM highlighted that supervised exercise training resulted in a substantial variation in responses in glucose homeostasis, insulin sensitivity, and mitochondrial muscle density, with approximately 15% to 20% of individuals failing to show improved metabolic health with exercise (Stephens & Sparks, 2015).

Traditionally, AE is the most-studied exercise. It recruits large groups of muscles and includes walking, cycling, swimming, and jogging (Yang et al., 2014). However, 80% of people with T2DM are overweight or obese and many have mobility problems, peripheral neuropathy, visual impairment, or cardiovascular disease. For this population, achieving the required volume and intensity of AE may not be easy, and resistance training may be more efficient (Sampath et al., 2018).

2.2. Resistance Training

Resistance training (RT) consists of performing exercises with resistance in order to achieve muscle contraction with the aim of improving the resistance and strength of muscle tissue. The Spanish Society of Sports Medicine (SEMEDE) highlights a series of general benefits that resistance training has on health, including increased muscle strength and power, increased bone mineral density, reduced risk of injury, improved sports performance, improved body composition

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in people with obesity or overweight, improved blood lipid profile, improved cardiovascular function, improved psychosocial well-being, and more (Sociedad Española de Medicina del Deporte. 2020).

RT induces muscle cell hypertrophy and increases strength but does not affect cells' biochemical composition. It is important to realize that, in terms of functional changes, significant strength gains can be obtained through changes in the nervous control of the muscle, mainly at the onset of a training program. In the beginning, functional changes can be achieved with a low level of structural change. As strength training continues, the muscles' cross-sectional area grows, a phenomenon which is more evident at the origin and insertion of the muscle (Narici et al., 1996).

Recent works suggest that RT results in effects similar to those elicited by AE. Indeed, RT can improve insulin action and glucose metabolism (Wojtaszewski et al., 2006) and stimulate mitochondrial biogenesis (Pesta et al., 2011).

One study found that in lean sedentary adults, both ten weeks of RT or of AE enhanced mitochondrial respiration in the skeletal muscle and that the increase in oxidative capacity was dependent on qualitative changes in mitochondria, as mitochondrial density did not undergo substantial changes (Pesta et al., 2011). This suggests that mitochondrial biogenesis is stimulated by both types of training, though it is unlikely that they achieve the same outcome through identical mechanisms.

RT is associated with a significantly lower risk of T2DM, regardless of whether or not AE is performed (Grøntved et al., 2012). In addition, several studies have shown that RT reduces the percentage of glycated hemoglobin, increases glucose elimination, and improves metabolic and lipid profiles, thus decreasing the risk of cardiovascular disease in patients with T2DM and reducing the risk of developing IR (Zanuso et al., 2010).

Hernán Jiménez et al., (2011) investigated whether an 8-week RT program with weights would lead to improvements in insulin sensitivity, lipid profile, and body composition in subjects with overweight or obesity. The authors proposed a randomized study on the intervention with 16 young subjects with overweight or obesity. They divided the participants into an experimental group (n=8), which participated in the

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8-week weight training program, and a control group (n=8), which did not take part in the training program. At the end of the intervention, they observed that participants in the experimental group had an 18% decrease in IR, measured via the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) index; a 10% decrease in low density lipoprotein (LDL) values; a 13% decrease in the arterial index; and an 8% increase in the concentrations of high-density lipoprotein cholesterol (HDL). In contrast, no significant differences were found in the endomorphic, mesomorphic, and ectomorphic components that make up the individuals' somatotype, somatic chart, and somatotypic distance or in body composition (Hernán Jiménez et al., 2011).

Another study by Crist-Roberts et al. sought to compare the effects of RT in subjects with T2DM and subjects without T2DM. They carried out an 8-week training protocol in order to compare insulin signaling, GLUT4 expression, and glycogen synthase activity as well as the protocol's effect on insulin sensitivity. As in the study conducted by Hernán Jiménez et al. in 2011, no significant differences in BMI or body composition were observed among participants after the program, but an acute effect of training on the ability to eliminate glucose via an insulin-dependent metabolic pathway was observed in diabetic and non-diabetic subjects during exercise. This was not the case at baseline, where no major changes were observed in diabetic subjects. This acute effect is due to the fact that the increase in muscle contractile activity during exercise increases expression of the GLUT4 protein and increases glycogen synthase enzyme activity. The action on GLUT4 improves the transport of glucose to the muscle and, thanks to glycogen synthase, glycogen synthesis capacity is greatly increased once the glucose reaches the muscle fiber (Christ-Roberts et al., 2004).

In both studies, it was observed that an intervention consisting of an 8-week RT protocol in subjects with obesity and T2DM produced large improvements in skeletal muscle cell insulin sensitivity and glucose transport. Nevertheless, in both studies, subjects' body composition did not change after the RT intervention.

This may lead us to make the mistake of thinking that although RT will directly produce large improvements in insulin sensitivity and transport mechanisms, it will not improve individuals' body composition. However, a study published in 2016 observed improvements in

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participants' body composition following a 12-week RT protocol carried out in order to measure its effects on insulin sensitivity, body composition, and fat tissue deposits in the body. The author concluded that the 12-week RT protocol, which involved moderate intensity exercise, had beneficial effects on insulin sensitivity and body composition, given that there were significant improvements in these parameters (principally a reduction in percentage of fat mass and increase in percentage of muscle mass; Langleite et al., 2016).

In another recent study, 257 middle-aged women were selected to test the effects of RT on body composition. Dual-energy x-ray absorptiometry was used to assess the women's body composition before and after training. The results showed that for each day per week of RT performed, body fat was 1.3 percentage points lower and fat-free mass was 656 grams higher. The more time the women spent training intensively, the better their body composition was. Thus, the greater the number of days, the amount of time, and the effort the women spent on RT, the lower their body fat and the higher their fat-free mass was. No significant differences were found according to age or energy or protein consumption between groups (Burrup et al., 2018).

Skeletal muscle plays a very important role in IR, though there is still a great deal of controversy about what that role is. The main theories seem to indicate that it is based on the large storage capacity that skeletal muscle has for the free fatty acids that adipose tissue is unable to store due to excess energy. The skeletal muscle has a great capacity to store glucose in the form of glycogen. When exercise is performed, the glycogen is used as an energy source and this store is emptied. The muscles are then able to continue storing glucose (Sethi & Vidal-Puig et al., 2007). Therefore, when treating obesity, it is very important that there is no significant loss of muscle mass during the fat loss process.

In individuals with IR, insulin and blood glucose levels in peripheral tissues and the liver decrease when exercise is being performed, approaching levels observed in people without pathology. According to Colberg (2007), "Resistance and endurance exercise will produce improvements in insulin sensitivity and cardiorespiratory system, directly related to diabetes prevention" (Colberg, 2007). This is because during exercise, the muscle is able to increase its ability to

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consume glucose; this improvement can continue for several hours after training and often persists until the next day (Hamada et al., 2006). Post-exercise glucose uptake is mainly mediated by insulin-dependent glucose uptake whereas two pathways (muscle contraction and insulin) are involved during exercise (Di Meo et al., 2017).

Initially, it was thought that the aforementioned effects of RT on insulin sensitivity were due to the fact that muscle mass was directly proportional to insulin sensitivity, i.e., the greater the muscle mass, the greater the insulin sensitivity (Miller et al., 1984). Recently, however, studies have been performed on how RT produces an increase in insulin sensitivity through a multitude of variables, regardless of gains in muscle mass (Speakman & Selman 2003).

Advances in molecular biology have shown that insulin action is significantly improved in skeletal muscle after a physical activity program that includes RT, as there is an increase in GLUT4 protein content (Kirwan & Del Aguila, 2003). In addition, people who exercise regularly have increased activity of the enzymes involved in glucose transport (IRS, PI3-kinase, AKT-kinase; Kirwan & Del Aguila, 2003).

One of the most important adaptations of muscle mass after an RT protocol is an increase in GLUT4 protein concentration (Kirwan & Del Aguila, 2003). This plays a role in the increase in insulin sensitivity because GLUT4 is directly related to the rate of insulin-stimulated skeletal muscle glucose transport, as mentioned in section 1 (Sakamoto & Holman, 2008).

RT increases carbohydrate metabolism in normal skeletal muscle and is able to reverse IR induced by a high-fat diet by altering the activity of key insulin-signaling components such as Pl3K, PKC, and AKT (Krisan et al., 2004). Another important adaptation that occurs is stimulation of the synthesis of muscle glycogen (Di Meo et al., 2017). The storage of glucose in the form of glycogen is regulated by the kinase glycogen synthase-3β (GSK-3β) protein, which is a direct target of Pl3K/AKT. GSK-3β has been implicated in the pathogenesis of IR (Nikoulina et al., 2000). According to Case et al., “Strength training results in AKT stimulation of glycogen synthesis through inhibition of GSK-3β” (Case et al., 2011). All of these adaptations favor insulin sensitivity.

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Table 1. Research training programs

Author	Study period (months)	Interventions	Sample (n)	Mean Age (Years)	Exercise prescription
Christ-Roberts et al., 2004	2	Supervised AE	22	Control group (36 ± 2) Diabetic group (45 ± 4)	60% of their peak VO2 for 20 minutes on a stationary cycle ergometer three times per week. Duration and frequency were progressively increased to 70% of their peak VO2 for 45 minutes, four times per week.
Holten et al., 2004	2	Supervised RT No exercise	17	NA	Progressive RT exercises (leg press, knee extension, and hamstring curl). NA
Dunstan et al., 2005	12	High-intensity progressive resistance training (HIRT) No exercise	36	60-80	Supervised gymnasium-based training for six months followed by an additional six months of home-based training NA
Sigal et al., 2007	6	Combined Supervised RT Supervised AE No exercise	251	53.5 ± 7.3 53.9 ± 6.6 54.7 ± 7.5 54.8 ± 7.2	AE program plus RT program. Seven different exercises on weight machines each session. 60–75% maximum heart rate; three times per week. NA
Benson et al., 2008	2	HIRT No exercise	78	12.2 ± 1.3	Participants were prescribed two sets (eight repetitions per set) of 11 exercises targeting all the major muscle groups at high intensity. NA
Jennings et al., 2009	6	Combined Supervised RT Supervised AE No exercise	103	54.48 ± 7.6 52.84 ± 7.5 55.35 ± 7.4 56.33 ± 6.9	3 times per week. 3 times per week. 3 times per week. NA

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Table 1. (Continued)

Author	Study period (months)	Interventions	Sample (n)	Mean Age (Years)	Exercise prescription
Church et al., 2010	3	Combined Supervised RT Supervised AE No exercise	262	55.4 ± 8.3 56.9 ± 8.7 53.7 ± 9.1 58.6 ± 8.2	AE program plus RT program. Three times per week; each set consisted of ten to 12 repetitions. 50–80% maximum heart rate; 150 min per week. NA
Ku et al., 2010	3	Supervised RT Supervised AE No exercise	44	55.7 ± 6.2 55.7 ± 6.2 57.8 ± 8.1	40–45% maximum capacity; five times per week. Moderate intensity; five times per week. NA
Larose et al., 2011	6	Combined Supervised RT Supervised AE No exercise	251	53.5 ± 7.3 54.7 ± 7.5 53.9 ± 6.6 54.8 ± 7.2	AE program plus RT program. Two to three times weekly; two to three sets per exercise. 60% VO2 peak; 75% heart rate; three times per week. NA
De Oliveira et al., 2012	3	Flexibility training Supervised RT Supervised AE Combined	43	53.42 ± 9.8 54.10 ± 8.9 54.10 ± 8.9 57.90 ± 9.8	Stretching exercises. 50% 1RM; four sets of eight to 12 repetitions of seven exercises Cycling that increased from 20 minutes to 50 minutes Same intensity and half the volume of that in the AE and RT groups
Bacchi et al., 2012	4	Supervised RT Supervised AE	40	55.6 ± 1.7 57.2 ± 1.6	30–50% 1RM; three sets of ten repetitions. 60–65% maximum heart rate
Arslan et al., 2014	3	Supervised AE No exercise	64	53.5 ± 6.5 54.0 ± 9.4	75% maximum heart rate, 45 minutes per session NA
AbouAssi et al., 2015	8	Combined Supervised RT Supervised AE	196	50 50 50	AE program plus the RT program Three days per week, eight exercises, three sets/exercise, 8–12 repetitions/set Equivalent to 19.2 km/week (12 miles/week) at 75% peak O2 consumption

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Author	Study period (months)	Interventions	Sample (n)	Mean Age (Years)	Exercise prescription
Bucci et al., 2015	4	Supervised RT	46	Elderly women with obesity	Training sessions three times per week for 60 minutes
Madsen et al., 2015	2	High-intensity interval training (HIIT) No exercise	23	52 ± 2 52 ± 2	Exercise three times per week (10×60 seconds HIIT) over an eight-week period on a cycle ergometer NA
Zou et al., 2015	4	Lower body RT No exercise	56	71.9±0.5 71.4±0.9	Training sessions three times per week for 60 minutes NA
Langleite et al., 2016	3	Combined RT and AE	22	40–65	RT sessions and two spinning bike interval sessions under careful supervision weekly, for a total of four hours of intensive exercise.
Lima et al., 2017	3	Combined RT and AE	44	60-75	10 consecutive weeks with three sessions per week on alternate days for a total of 30 sessions.
Henriquez et al., 2017	6	Supervised AE Supervised RT	42	45-60	Moderate aerobic training with a braked cycle ergometer at 60–65% of their estimated maximal oxygen consumption, continuously during 40 minutes A low-load circuit resistance training protocol, performed until voluntary exhaustion, considered as the moment when the range of motion could not be completed, on six individual muscle groups (pectoralis, dorsal, biceps, triceps quadriceps, and gastrocnemius)
Son et al., 2017	3	Combined RT and AE No exercise	40	15 ± 1	The program was divided into warm-up (five minutes), the main exercise (30 minutes of various exercises and 20 minutes of playing badminton), and cool-down (five minutes). NA

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Table 1. (Continued)

Author	Study period (months)	Interventions	Sample (n)	Mean Age (Years)	Exercise prescription
Burrup et al., 2018	>12	Supervised RT No exercise	257	41.7 ± 3.0	Not described NA
Pourranjbar et al., 2018	2	AE No exercise	80	38.1±2.3 38.8±1.7	Three 45-minute sessions per week of AE training for eight weeks that included running at 50-70% of maximum heart rate and progressive intensity as the weeks went by. NA
Winding et al., 2018	3	HIIT AE No exercise	29	54±6 58±8 57±7	Ten one-minute intervals at 95% of peak workload interspersed with one minute of active recovery Three training sessions per week of either 40 minutes of cycling at 50% of peak workload or ten one-minute intervals at 95% of peak workload alternated with one minute of active recovery NA
Martins et al., 2018	3	HIRT Combined RT and AE	16	64.3 ± 6.7 65.0 ± 6.3	Ten 60-second sets of high-intensity exercise alternated with a 60-sec recovery period of low-intensity exercise 30-minute walk of moderate intensity following by five resistance exercises.
Micielska et al., 2019	2	High-intensity circuit training No exercise	33	38 ± 12	Three circuits of nine exercises with own body weight as a workload, three times per week for five weeks. NA

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Table 2. Objectives, results and conclusion of the studies we have researched

Author	Study aim	Results and conclusion
Christ-Roberts et al., 2004	To determine how improved insulin signaling, GLUT4 expression, and glycogen synthase activity contribute to improved insulin sensitivity after a training program.	• BMI • Individuals with diabetes had significantly higher levels of fasting plasma glucose, insulin, and hemoglobin A1c (HbA1c) than non-diabetics • Significantly increased insulin-stimulated glucose elimination
Holten et al., 2004	To investigate the effect of very low levels of RT on insulin action in skeletal muscle and glucose metabolism in patients with T2DM.	• Improved muscle strength in all subjects • 40% increase in plasma GLUT4 in trained muscles and increased expression of insulin receptors in skeletal muscle **Conclusion:** RT results in an increase in insulin action in skeletal muscles in patients with T2DM.
Dunstan et al., 2005	To examine whether improvements in glycemic control and body composition resulting from six months of supervised high-intensity progressive RT could be maintained after an additional six months of home-based RT.	• HbA1c decreased significantly more in the RT group (-0.8%) during six months of supervised gymnasium-based training; however, this effect was not maintained after an additional six months of home-based training. • The greater increase in lean body mass (LBM) observed in the RT group compared with the control group (0.9 kg, $p < 0.05$) after the gymnasium-based training tended to be maintained after the home-based training **Conclusion:** In older adults with T2DM, home-based progressive resistance training was effective for maintaining the gymnasium-based improvements in muscle strength and lean body mass but not glycemic control. Reductions in adherence and exercise training volume and intensity seem to impede the effectiveness of home-based training for maintaining improved glycemic control.
Sigal et al., 2007	To determine the effects of AE alone, RT alone, and combined exercise training on hemoglobin A1c values in patients with T2DM.	• Improvements in the hemoglobin A1c value in the AE, RT, and combined group. **Conclusion:** Either AE or RT alone improves glycemic control in type 2 diabetes, but the improvements are greatest with combined AE and RT.
Benson et al., 2008	To examine whether HIRT (eight weeks, twice a week) would decrease central adiposity in children, as assessed via waist circumference.	• Significantly improved waist circumference, fat mass, percent body fat, BMI. Upper body strength and lower body strength **Conclusion:** Isolated HIRT significantly improves central and whole body adiposity in association with muscle strength in normal-weight and overweight children.

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Table 2. (Continued)

Author	Study aim	Results and conclusion
Jennings et al., 2009	To determine the effects of AE and RT and the incremental effect of combined AE and RT on resting metabolic rate (RMR) in previously sedentary individuals with T2DM	• RMR did not change significantly in any group after accounting for multiple comparisons despite significant improvements in peak oxygen consumption and muscular strength in the exercising groups. Adjusting RMR for age, sex, fat mass, and fat-free mass in various combinations did not alter these results **Conclusions:** RMR was not significantly changed after a 6-month exercise program, regardless of modality, in this sample of adults with T2DM.
Church et al., 2010	To examine the benefits of AE alone, RT alone, and a combination of both on hemoglobin A1c (HbA1c) in individuals with T2DM	• The mean changes in HbA1c were not statistically significant in either the RT (−0.16%; 95% CI, −0.46% to 0.15%; $p = 0.32$) or the AE (−0.24%; 95% CI, −0.55% to 0.07%; $p = 0.14$) groups compared to the control group. • Only the combination exercise group improved maximum oxygen consumption (mean, 1.0 mL/kg per min; 95% CI, 0.5-1.5, $p < 0.05$) compared to the control group. • All exercise groups reduced waist circumference. • The RT group lost a mean of −1.4 kg fat mass (95% CI, −2.0 to −0.7 kg; $p < 0.05$) and combination training group lost a mean of −1.7 (−2.3 to −1.1 kg; $p < 0.05$) compared to the control group. **Conclusions**: Among patients with T2DM, a combination of AE and RT improved HbA1c levels compared to the nonexercise control group. This was not achieved by AE or RT alone.
Ku et al., 2010	To examine the effects of RT on acute phase reactants, cytokines, and adipokines, which may present an opportunity for improved management of T2DM.	• AE induced a greater body weight loss in comparison to the RT group and the control group • Overall fat mass of the whole body was reduced in both exercise groups, but the change was significantly greater in the AE group. • RT was related to a greater increase in muscle strength compared with AE. • Leptin levels decreased significantly by 37.8% (from 9.86 ± 3.06 to 6.13 ± 4.00 ng/ml, $P < 0.001$) and adiponectin increased significantly by 75.1% (from 3.86 ± 2.00 to 6.76 ± 1.24 ng/ml, $P < 0.001$) in the AE group. In the RT group, leptin levels did not change significantly after the intervention, although there was a significant increase in adiponectin of 46.2% (from 4.98 ± 2.52 to 7.28 ± 3.72 µg/ml, $P = 0.002$). • The change in plasma RBP4 concentration was significantly positively correlated with that of SFAT ($r = 0.664$, $P = 0.013$) in the RT group, but there was no statistically significant correlation in the AE group ($r = −0.405$). The changes in kITT and HbA1c showed no statistically significant differences between the groups.

Author	Study aim	Results and conclusion
		Conclusions: RT did not alter intramuscular adipose tissue but did reduce plasma RBP4 levels without improving insulin sensitivity.
Larose et al., 2011	To investigate if reductions in $HbA_1(c)$ would be related: (1) to increases in aerobic fitness and strength respectively in patients performing AE or RT; and (2) to changes in strength and aerobic fitness in patients performing AE and RT.	• AE: Significant associations were found between changes in both VO_2(peak; p = 0.040) and workload (p = 0.022), and changes in $HbA_1(c)$. • Combined training: Improvements in VO_2(peak; p = 0.008), workload (p = 0.034), and ventilatory threshold (p = 0.003) were significantly associated with changes in $HbA_1(c)$. • RT: Increases in strength on the seated row (p=0.006) and in mid-thigh muscle cross-sectional area (p = 0.030) were significantly associated with changes in $HbA_1(c)$. **Conclusions:** There appears to be a link between changes in fitness and $HbA_1(c)$. The improvements in cardiorespiratory fitness with AE may be a better predictor of changes in $HbA_1(c)$ than improvements in strength.
De Oliveira et al., 2012	To show the response of some metabolic control parameters, antioxidant activity, and oxidative stress markers after 12 weeks of training with three different exercise protocols in subjects with T2DM.	• There was a decrease in fasting plasma glucose and HbA1c in the RT group. • Cortisol levels were lower (p = 0.034) in the AE group than in the no exercise group after training • There was an incremental increase in VO2peak only in the AE group, proving the efficiency of the training performed by this group ($p < 0.05$). **Conclusions:** Exercise training selectively increased antioxidant enzymes in the AE group, offering additional protection against oxidative stress in subjects with T2DM. We suggest that this response could be a result of transitory increases in ROS production mediated by exercise and that AE provides protection against the constant oxidative attack that affects subjects with T2DM.
Bacchi et al., 2012	To assess differences between the effects of AE and RT on HbA(1c; primary outcome) and several metabolic risk factors in subjects with T2DM and to identify predictors of exercise-induced metabolic improvement.	• HbA(1c) was similarly reduced in both groups. • Total and truncal fat, VAT, and SAT were also similarly reduced in both groups whereas insulin sensitivity and lean limb mass were similarly increased. • β-Cell function showed no significant changes. In multivariate analyses, improvement in HbA(1c) after training was independently predicted by baseline HbA(1c) and by changes in VO2peak and truncal fat. **Conclusions:** RT, similarly to AE, improves metabolic features and insulin sensitivity and reduces abdominal fat in patients with T2DM. Changes after training in VO2peak and truncal fat may be primary determinants of exercise-induced metabolic improvement.

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Table 2. (Continued)

Author	Study aim	Results and conclusion
Arslan et al., 2014	To know about the impact of AE on malondialdehyde (MDA) and tumor necrosis factor alpha (TNF-α) in DM.	• BMI and class of treatment for diabetes were not different between groups. • While soluble TNF-α remained essentially unaffected by physical training, plasma concentrations of MDA markedly decreased ($p < 0.05$). Physical training also decreased body weight, waist circumference, and blood pressure ($p < 0.05$). **Conclusions:** Exercise training favorably affected body weight, waist circumference, and blood pressure. A 12-week aerobic-training program performed three times per week without a concomitant weight loss diet was associated with significant decrease in MDA levels in individuals with T2DM.
AbouAssi et al., 2015	To compare the effects of AE, RT, and combined training on the action of insulin in both its acute and chronic phases.	• A significant increase was observed in post-training insulin sensitivity in combination training with respect to AE or RT. • A significant increase in the percentage of muscle mass with decrease in fat mass was observed in the RT group only. **Conclusions:** Combined training showed much better results in improving insulin sensitivity and long-term glucose basal levels than RT or AE alone.
Bucci et al., 2015	To test the effects of RT on insulin sensitivity in obese mothers and elderly women with IR.	• Improved lower body muscle cross section. • No significant changes in BMI, IR, blood glucose, or percent fat. • Improved insulin response in post-menopausal women. **Conclusions:** High maternal BMI predisposes skeletal muscle to IR in older offspring. Regular physical activity can help reduce its health effects by improving insulin sensitivity
Madsen et al., 2015	To investigate glycemic control, pancreatic function, and total fat mass before and after eight weeks of low volume HIIT on a cycle ergometer in patients with T2DM.	• Whole body insulin sensitivity as determined by the disposition index (DI) was significantly increased ($p = 0.03$). • The glucose continuum was significantly reduced at -15 ($p = 0.03$), 30 ($p = 0.03$), and 120 minutes ($p = 0.03$) and at -10 ($p = 0.003$) and 0 minutes ($p = 0.003$) with an additional improvement ($p = 0.03$) of its 1st phase (30 minutes) area under the curve (AUC). • Significant abdominal fat mass losses were seen in both groups. **Conclusions:** HIIT improves overall glycemic control and pancreatic β cell function in patients with T2DM. Additionally, both groups experienced abdominal fat mass losses. These findings demonstrate that HIIT is a beneficial exercise strategy that is beneficial for the health of patients with T2DM.
Zou et al.,	To investigate whether or not maternal	• The overweight group had lower thigh muscle insulin sensitivity compared with the normal/lean

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Author	Study aim	Results and conclusion
2015	obesity influences insulin sensitivity and its. relationship with leucocyte telomere length (LTL) in elderly women	weight group ($p = 0.048$) but similar whole body insulin sensitivity. • RT improved whole body and skeletal muscle insulin sensitivity in the overweight group only ($p = 0.004$ and $p = 0.013$, respectively) and increased muscle mass in both groups. **Conclusions:** Maternal obesity and having telomere shortening were associated with IR in adult offspring. A RT program may reverse this disadvantage among offspring of obese mothers
Langleite et al., 2016	To investigate the effect of exercise on insulin sensitivity, body composition, and fat deposits in sedentary men with or without overweight and dysglycemia.	• Insulin sensitivity, VO2max, strength, whole body fat and muscle content, and abdominal fat deposits were improved, with no obvious differences between men with and without dysglycemia. **Conclusions**: Body composition, fat distribution, and insulin sensitivity improved after RT.
Lima et al., 2017	To compare the effects of the combination of AE and RT with those of isolated AE on blood pressure, body composition and insulin sensitivity in older adults.	• Significant reductions in BMI, abdominal and waist circumference, and blood pressure in both groups. • Fat mass was reduced more in the combined group. • No significant differences in insulin sensitivity. **Conclusions:** Similar effects between both types of training were observed, though combined training is more effective in reducing percentage of fat than AE alone.
Lima et al., 2017	To compare the effects of the combination of AE and RT with those of isolated AE on blood pressure, body composition and insulin sensitivity in older adults.	• Significant reductions in BMI, abdominal and waist circumference, and blood pressure in both groups. • Fat mass was reduced more in the combined group. • No significant differences in insulin sensitivity. **Conclusions**: Similar effects between both types of training were observed, though combined training is more effective in reducing percentage of fat than AE alone.
Henriquez et al., 2017	To compare the effects of a low-load circuit RT protocol and usual AE in postmenopausal women	• Women in both groups experienced significant reductions in blood pressure and in total body, subcutaneous, and intra-abdominal body fat. • Reductions in total cholesterol and triacylglycerol levels were also observed. • No changes in IR indexes, 8 isoprostanes, C-reactive protein, or interleukin 6 were observed in either group. **Conclusions**: We conclude that low-load circuit RT and AE resulted in the same reductions in body fat and serum lipid levels

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Table 2. (Continued)

Author	Study aim	Results and conclusion
Son et al., 2017	To examine the impact of combined resistance and aerobic exercise (CRAE) training on blood pressure, brachial-ankle pulse wave velocity (baPWV), IR, and body composition in girls with obesity and pre-hypertension.	• Blood pressure, pulse wave velocity, ET-1, nitrite/nitrate, HOMA-IR, percent body fat, and waist circumference were significantly improved ($p < 0.05$) in the exercise group after 12 weeks of training versus the control group. **Conclusions:** This study provides evidence that CRAE can be a useful therapeutic treatment for high blood pressure, IR, and central adiposity, thereby reducing the likelihood of pathological development of cardiovascular diseases in later adulthood.
Burrup et al., 2018	To investigate the effects of RT on body composition	• For each day per week of RT performed, body fat was 1.3 percentage points lower and fat-free mass was 656 g higher. **Conclusions:** The more days, time, and effort women devote to strength training, the lower their body fat and the higher their fat-free mass is.
Pourranjbar et al., 2018	To evaluate the effects of eight weeks of AE on serum levels of myonectin and IR in women with overweight and obesity.	• Serum levels of myonectin in the experimental group increased significantly ($p = 0.000$); however, IR decreased significantly in the experimental group ($p = 0.000$). **Conclusions:** exercise training can play an essential role in decreasing obesity-related diseases and metabolic syndrome; this effect is partly related to the roles of myonectin. Therefore, the use of this type of exercise is recommended to reduce the risk of diseases associated with obesity and metabolic syndrome.
Winding et al., 2018	To evaluate whether HIIT with a lower time commitment can be as effective as endurance training (END) on glycemic control, physical fitness, and body composition in individuals with T2DM.	• Increased VO2 peak, more so in the HIIT group. • HIIT decreased whole body and android fat mass compared to the control group. In addition, visceral fat mass, HbA1c, fasting glucose, postprandial glucose, glycemic variability, and HOMA-IR decreased after HIIT. **Conclusions:** HIIT resulted in similar or even better improvements in physical fitness, body composition, and glycemic control compared to AE. HIIT therefore appears to be an important time-efficient treatment for individuals with T2DM.
Martins et al., 2018	To compare the effects of 12 weeks of high-intensity interval body weight training (HIRT) with combined training.	• Both groups increased ($p < 0.05$) muscle mass index, 6MWT, and interleukin 1 receptor antagonist and decreased fasting glucose, glycated hemoglobin, insulin, HOMA-IR, and monocyte chemoattractant protein-1. • There was a significant ($p < 0.05$) interaction of time by the group in muscle strength, indicating that only the combined training group increased muscle strength. **Conclusions**: Changes in HOMA, IL-1ra, 6MWT, and muscle mass index with HIRT are similar when compared to combined training for individuals at high risk of T2DM.

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Author	Study aim	Results and conclusion
Micielska et al., 2019	To investigate the effect of a single and 15 units of high-intensity circuit training (HICT) program on glucose metabolism, myokine response, and selected genes' expression in women.	• The following parameters tended to decrease after the 5-week HICT program: insulin and HOMA-IR. Training decreased the insulin/IGF-1 ratio (51% CI: -63% to -34%) and led to a drop in myostatin concentration that was significant only among middle-aged women and at baseline insulin resistance. **Conclusions:** HICT improved insulin sensitivity and decreased myostatin concentration among older, insulin-resistant women with lower baseline physical capacity.
Yan et al. 2019 (Yan, J. et al. 2019)	To examine the effects of RT relative to AE on abdominal adipose tissue and metabolic variables in adults with prediabetes.	• Increase in muscle mass was greater in the RT group than in the AE and control groups. • Fasting plasma glucose decreased significantly in the RT and AE groups. • No significant differences were observed in lipid, waist-to-hip ratio, BMI, fasting insulin, 2-hour postprandial glucose, HbA1c, HOMA-IR, and HOMA-β across groups. **Conclusions:** Both AE and RT are effective in reducing abdominal adipose tissue and fasting plasma glucose in adults with prediabetes. Importantly, RT, but not AE, is effective in augmenting muscle mass.

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It has been observed in several studies that a single round of RT results in increased AMPK activity (Dreyer et al., 2006). This transient activation of AMPK leads to phosphorylation of several key proteins in multiple metabolic pathways, resulting in increased ATP production in fatty acid oxidation and glucose uptake processes, which increases the translocation of GLUT4 (Mu et al., 2001).

Another important adaptation responsible for the insulin-sensitizing effect of RT, independent of the increase in lean mass, is an increase in insulin receptor protein expression (Holten et al., 2004).

These adaptations are key in restoring metabolic flexibility in subjects with IR, pre-diabetes, or T2DM. RT will therefore be of great importance, as it helps stimulate glucose transport via insulin-dependent pathways and appears to protect against mitochondrial dysfunction (Di Meo et al., 2017).

3. Types of Physical Activity to Reduce Insulin Resistance

The aforementioned research examined the effectiveness of physical exercise as a treatment for people with IR and overweight/obesity. We also investigated whether there were differences in benefits among different types of training (RT, AE, and combined). Indeed, greater improvements were observed in subjects who combined RT with AE (combined training) compared to those doing RT or AE alone. AE alone yielded the fewest improvements.

Subjects who did combined exercise showed greater improvements in HbA1c than those who did supervised AE or supervised RT alone; however, the decrease in some cardiovascular risk factors was less marked. In terms of weight loss, there were no significant differences among the combined, supervised AE, and supervised RT forms of exercise.

This evidence suggests that to maximize the benefits for individuals with IR, the best intervention is a training program that concurrently combines RT and AE. According to the literature, an intervention based mainly on RT and supplemented with AE is preferable over an intervention based mainly on AE and supplemented with RT. If the aim

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is to improve insulin sensitivity, skeletal muscle strength should always be worked as a fundamental and obligatory pillar of the training program.

There are several articles shown in Table 1 and Table 2 that found no significant differences in the short term between a RT program and an AE program and thus conclude that we should not prioritize one over the other. However, there is a fundamental difference between the two types of training. RT produces significant increases in muscle mass and improves quality of muscle tissue—an effect that AE does not produce—and skeletal muscle mass is the key tissue when it comes to preventing and reducing the risk of suffering from T2DM.

3.1. Intensity of Resistance Training

As seen above, RT—and, above all, combined training—offers significant benefits in terms of IR and the overall health of individuals with IR. Given this premise, several studies have aimed to determine the most effective training intensity to optimize these benefits.

Evidence suggests that RT produces qualitative improvements in muscle mass regardless of the intensity of the exercises. Holten et al., (2004) sought to evaluate how low-intensity RT affects insulin levels in skeletal muscle and glucose metabolism in subjects with T2DM. After training, all subjects had improved muscle strength, but no changes were observed in fasting plasma glucose, insulin, or peptide concentrations after the training protocol. GLUT4 concentrations were 40% higher in the trained muscles and there was also an increase in the expression of insulin receptors in skeletal muscle. The authors concluded that RT, even at low intensity and at a very low dose, results in an increase in insulin action in skeletal muscle in patients with T2DM and that this effect was probably not caused by increased muscle mass alone, according to muscle biopsy data (Holten et al., 2004).

Two studies investigated the intensity of RT most suitable for achieving benefits in insulin sensitivity and body composition. In the first study, Benson et al., (2008) carried out a protocol of high-intensity progressive strength training, with loads close to 80% of the participants' one-repetition maximum (Benson et al., 2008). In the

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other, Dustan et al. carried out both a high-intensity progressive strength training protocol and low-intensity progressive strength training protocol were performed consecutively over the course of 12 months (Dunstan et al., 2005).

Benson et al., (2008) state that no studies that involved low-intensity progressive strength training protocol in isolation show similar benefits to those achieved through a high-intensity progressive strength training protocol. Thus, they conclude that high-intensity strength training (HIST) produces very significant improvements in insulin sensitivity and body composition that are greater than improvements obtained with a low-intensity progressive strength training (LIST) protocol, in which improvements in insulin sensitivity do occur, but to a lesser degree (Benson et al., 2008).

Dunstan et al., (2005) conducted a 12-month intervention. The first six months consisted of HIST, after which large improvements in insulin sensitivity and body composition were observed in the participants. In the following six months, a LIST protocol was carried out with the aim of analyzing whether the benefits achieved by HIST during the first six months were maintained. The authors found that during LIST, the benefits in terms of glycemic control achieved after the HIST protocol were maintained. However, there was a large difference in body composition between HIST and LIST, with high-intensity training being much more effective than low-intensity training (HIST>LIST) in improving participants' body composition (Dunstan et al., 2005).

On the other hand, another study sought to compare the effects of either a LIST protocol or regular AE in postmenopausal women. Regardless of the type of training, the subjects lost weight, reduced blood pressure, and decreased fat mass, though there was a somewhat more significant decrease in abdominal and subcutaneous fat in the LIST group. No significant changes in insulin sensitivity or inflammatory or oxidative stress parameters were observed in either group (100).

The three aforementioned studies suggest that the protocols that lead to greater improvements in insulin sensitivity, glycemic control, and body composition in the long-term are HIST protocols. Furthermore, they indicate that a LIST protocol produces greater improvements in these parameters compared to an AE protocol, even

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though the effects are not as marked as those obtained via HIST protocols (Dunstan et al., 2005; Benson et al., 2008; Henriquez et al., 2017). Therefore, it can be concluded that priority should be given to high-intensity RT followed by low-intensity RT, and, finally, AE.

In conclusion, the literature analyzed suggests that RT, regardless of the intensity at which it is performed, produces important improvements in insulin sensitivity and body composition and that the longer the duration of the RT protocol, the greater these improvements are. Therefore, RT should be a mainstay in the management of IR in people with overweight or obesity and should always be included as a central, fundamental intervention in any training program, regardless of its intensity.

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Chapter 4

PHYSICAL EXERCISE AND HIGHER BRAIN FUNCTIONS: COGNITIVE AND EMOTIONAL BENEFITS

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ABSTRACT

Physical exercise has been recommended for the maintenance of physical and mental health, and prevention or attenuation of some diseases development due to motor activity. It is capable of inducing plastic and dynamic changes in the central nervous system (CNS), in order to favor the neurogenesis,

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synaptogenesis and angiogenesis, besides contributing to the synaptic modulation. In this perspective, besides the cardiovascular protection, the practice of physical exercise has several benefits by stimulating the neuroprotection against several insults, such as stroke, cognitive decline, progression of neurodegenerative diseases and others. It has been suggested by *in vivo* studies that physical exercise acts in the CNS triggering several biological processes, such as; reduction and prevention of oxidative stress, increasing neuronal communication, improving cell metabolism, decreasing or inhibiting inflammatory processes, modulating the expression of neurotrophins and affecting positively the synaptic communications. On one hand we have neurological and psychiatric diseases that have as common features, those targets of physical exercise in the CNS, such as depression, anxiety, motor dysfunctions and cognitive decline, while on the other, we have that physical exercise can modulate those cellular processes and mitigate these disorders. In this chapter, we are going to highlight experimental evidence that may support clinical evidence already described in the literature that characterize physical exercise as a strong promoter of well-being and health of the CNS.

Keywords: physical exercise, cognition, emotions

INTRODUCTION

The clear distinction of physical activity and physical exercise is fundamental to initiate the discussion about the beneficial effects of physical exercise. The former, is any and all body movement that we perform in our daily routine, such as bathing, sweeping, cooking, walking, in short, any movement performed by the contraction of skeletal muscles that involves greater energy expenditure than resting levels, while physical exercise requires a physical effort of the body with much greater energy expenditure comparable to the levels of rest, translating as planned, structured and repetitive physical activity with clear objectives in maintaining the health and general well-being of individuals (Dishman et al., 1988; Hassmen et al., 2000; WHO, 2010; Scully et al., 1998).

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Continuous exercise is one of the factors that promotes a healthier lifestyle. It is a parameter on physiological conditions such as cardiac activity, temperature, blood pressure, respiratory rate and muscle activity, that are related to a healthy organism (Hueston et al., 2017; Wilmore & DL, 2001; Wilmore, 2001). Physical exercise has the ability to induce changes in the body composition and lipid profile; it promotes the maintenance of glycemic homeostasis, increasing peripheral insulin sensitivity and glucose capitation; provides psychological benefits confirmed in patients with mild to moderate depression; it favors social integration and improves self-esteem, *i.e.,* it acts by improving the psychosocial state in general of individuals (Duman, 2005).

Some studies show that regular physical exercise reduces lifestyle-related disorders (Radak et al., 2006), reduces the risk of cancer (Patel et al., 2008) and risk of strokes, as well as the mortality related to them (Lee & Paffenbarger Jr, 1998; Tahamtan et al., 2013); it improves age-related neuronal loss and is currently recommended as a therapeutic aid in several neurodegenerative diseases (Farzana et al., 2013); it promotes improvement of cognitive functions (Di Wang et al., 2018; Farzi et al., 2018; Shen et al., 2013); and it induces neuroprotection through its anti-inflammatory effect (Chennaoui et al., 2008; Gomes da Silva et al., 2013).

In addition to the effects of physical exercise on various organ systems, some authors suggest a correlation between increased aerobic capacity and improved cognitive functions (Arida et al., 2011; Kramer et al., 1999; Laurin et al., 2001). According to Gómez-Pinilla (2008), this beneficial effect is justified by hormonal changes, the release of neurotransmitters and the activation of specific receptors in response to physical exercise.

Research on animal models, using a physical exercise paradigm, attempt to simulate the stress conditions observed in humans, in order to better assess or monitor systemic, cellular and molecular changes resulting from physical training. Among these paradigms, forced and voluntary exercise are used. Among the forced types the most widely used are treadmill running and swimming. The voluntary exercise paradigm uses a sliding wheel placed in the animal's environment, which can be freely use (Ang & Gomez-Pinilla, 2007). The advantage of the running wheel defended by some studies, is that the results can

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be applied to human conditions when the individuals choose how much and when to run. However, it cannot be easily quantified and standardized regarding the frequency, speed, duration and intensity, as with the forced paradigm. In addition to facilitate the measurement and standardization of its variables, forced exercise is close to the protocols used in human rehabilitation therapies (Ang & Gomez-Pinilla, 2007).

NEUROBIOLOGICAL BASES OF PHYSICAL EXERCISE BENNEFITS

Understanding that physical exercise benefits several organ systems, different modalities such as swimming, acrobatic or voluntary exercise, treadmill and others, of high or low intensity, intermittent or continuous, of short or long duration, have been used to evaluate their effects on brain function (Arida et al., 2007). In this way, it is understood that the regular practice of physical exercise can be used as a preventive and therapeutic resource for health (Perrey, 2013), capable of reducing morbidity and mortality rates (WHO, 2010).

Unlike the sedentary lifestyle that is associated with numerous pathologies, physical exercise has been relevant to the fight against neurological and neurodegenerative diseases, as well as the attenuation of neural responses to oxidative stress and immunodepression (Arida et al., 2007; WHO, 2010). Therefore, the neuroprotective effects of physical exercise have gained great importance in the last few decades by studies with humans and experimental models.

Studies with physical exercise have shown increased brain metabolism, promoting plasticity, neurogenesis and angiogenesis (Aguiar Jr. & Pinho, 2007), reflecting into structural and functional changes in CNS (Berchicci et al., 2014; Davranche et al., 2006; Garcia et al., 2012). In this perspective, some benefits regarding the amelioration of Alzheimer’s and Parkinson’s diseases progression have been evidenced (Archer, 2011; García-Mesa et al., 2011; Paillard et al., 2015; Tanaka et al., 2009), moreover, it has been pointed as capable of reducing the risk of chronic and metabolic diseases with

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inflammatory features, due to its anti-inflammatory effects (Cadet et al., 2003; Spielman et al., 2016; Svensson et al., 2015).

Physical exercise positively influences the restoration of brain function, providing better learning, memory and neuroplasticity, both in the healthy and damaged brain (Klintsova et al., 2012). Because of its capacity of inducing physiological, biochemical and psychological changes, it can be seen as a non-pharmacological intervention for the treatment of disorders related to psychobiological aspects, such as depression, anxiety and chemical dependence (De Mello et al., 2013; Wang et al., 2014). Thus, studies reinforce the hypothesis that physical exercise is favorable in both physical and psychological spheres due to the fact that activity in moderately active people causes a lower risk of developing disorders when compared to sedentary ones (Accattato et al., 2017; Guimaraes et al., 2008).

As mentioned above, physical exercise promotes neuroplasticity, which is a dynamic process also described as an adaptive process by which the CNS reorganizes itself. This is fundamental for tissue repair, as well as for functional aspects, such as memory, learning and motor functions (Cassilhas et al., 2016; Hötting & Röder, 2013). Neuroplasticity as a neuroprotective mechanism acts on numerous variables capable of promoting neuron regeneration and survival, as well as the upregulation of neural growth factors, which provide protection to the CNS through the growth and development of new neurons (Fabel et al., 2009; Nokia et al., 2016; Van der Borght et al., 2009). However, although studies encourage the practice of physical exercise as a goal for the conservation or improvement of the CNS, through neuroplasticity, there is still no clear understanding for this mechanism (Perrey, 2013).

Physical exercise influences neural plasticity, by promoting biological and physical-chemical changes, as well as modulation of the expression of neurotrophic factors and CNS oxygenation (Fernandes et al., 2018; Perrey, 2013). Several studies demonstrate the influence of physical exercise on synaptic plasticity by the ability to induce gene expression associated with synaptogenesis, structural support and signal transduction. Moreover, physical exercise increases the expression of growth factors as brain-derived neurotrophic factor (BDNF) (Berchtold et al., 2005; Brandt et al., 2010; Ke et al., 2011),

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nerve growth factor (NGF) (Neeper et al., 1996), glia-derived neurotrophic factor (GDNF) (Smith & Zigmond, 2003) and others. The increased expression of these growth factors modulates apoptotic pathways inhibiting cell death, stimulating the growth and genesis of new cells. Physical exercise also demonstrates a positive modulatory effect on endogenous cytokine levels (Ang & Gomez-Pinilla, 2007), as proinflammatory cytokines [tumor necrosis factor (TNFα), interleukin 1a (IL1a), interleukin 1b (IL1b), interleukin 6 (IL6)], that in a pathological condition, would drive to neuroinflammatory processes (Chennaoui et al., 2008).

We must consider the paradox regarding the effects of physical exercise: the pro-oxidant capacity. It increases oxygen consumption and the generation of reactive oxygen species (Navarro & Boveris, 2010). This fact could be disastrous if the synthesis of antioxidant enzymes, such as superoxide dismutase (Higuchi et al., 1985; Leeuwenburgh et al., 1997), catalase (Oh-ishi et al., 1997; Quintanilha, 1984) and glutathione peroxidase (Ji, 1995), does not occur in parallel. However, physical exercise generates an adaptation of the antioxidant system, with increased activity of regulatory enzymes providing an increase in resistance against stress and consequently reduction of oxidative damage (Kandola et al., 2016; Leeuwenburgh et al., 1997; Powers et al., 1994). All these modulation pathways can interfere with different brain functions. Next, we will discuss the evidence of the elected functions to be addressed in this chapter.

Modulation of Cognitive Functions by Physical Exercise

Cognition consists of a set of functions displayed by the CNS, that is involved in communication, vision, memory, learning, decision-making and even emotions (Robbins, 2011; Vaynman et al., 2004). In this way, several anatomical structures are involved such as the hippocampus, somatosensorial cortex, basal ganglia and others (Culpepper, 2015). As mentioned above, some studies have suggested that physical exercise may affect several organizational levels in tissue structure, such as modulation of gene expression, biochemical

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parameters, neurotransmission, cell survival and proliferation, and morphology, which can possibly drive to functional modulation.

The evidence about the modulation of cognitive functions by physical exercise are still limited and with no consensus about the outcomes of the different physical exercise intensities. Moreover, there is a lack of evidence to discuss by which mechanisms physical exercise may act to play a beneficial role on cognition. However, several pre-clinical studies lead us to understand that the neuroplasticity, oxidative biochemistry balance and vascular improvement are associated with the positive effects.

Some experimental evidences have shown that physical exercise plays a dual role in hippocampal structure: angiogenic and neurogenic. The angiogenic action is associated with the vascular endothelial growth factor A up-regulation (Morland et al., 2017), which influences the neurogenesis and synaptic function (De Rossi et al., 2016). In addition to that, the expression of Insulin Growth Factor – 1 (IGF1) is related to the maturation of new blood vessels and also seems to be positively modulated by physical exercise (Carro et al., 2000; Jacobo & Kazlauskas, 2015; Nakamura et al., 2010).

The IGF1 also acts as a neurotrophic factor in the hippocampus of rats submitted to physical exercise (Llorens-Martín et al., 2010), participating in the different stages of neuron differentiation and survival. Moreover, aerobic physical exercise increases serum and hippocampal levels of IGF1 in rats, associated with a better memory and learning performance (Cetinkaya et al., 2013). Futhermore, an increase in neuronal cell numbers in CA1, CA3 and dentate gyrus by moderate aerobic physical exercise (Uysal et al., 2005) has also been observed. Another factor intrinsically associated with hippocampal neuroplasticity and functions is the levels of BDNF in the hippocampus as observed in previous reports (Aguiar et al., 2011; Baj et al., 2012; Oliff et al., 1998) by increasing the neurogenesis and inducing changes on glial cells (Fahimi et al., 2017; Mee-Inta et al., 2019). These factors together have improved cognitive functions in rats in several models of physical exercise, reinforcing the important role of physical exercise on neuroplasticity.

Besides that, in clinical evidence, physical exercise is often associated with the increase of hippocampal volume (Erickson et al.,

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2011; Niemann et al., 2014; Thomas et al., 2016) and a possible tool for preventing cognitive decline. A recent systematic review concluded that moderate physical exercise improves cognitive function after analysing primary studies which evaluated several cognitive domains (Fernandes et al., 2018), such as reaction time and working memory (Lo Bue-Estes et al., 2008; Olson et al., 2016). A meta-analysis (Groot et al., 2016) showed a positive association between physical exercise and cognitive function in patients with dementia, emphasizing the value of aerobic exercise for this achievement. Moreover, it was also observed in another meta-analysis of randomized controlled trials of patients with Alzheimer's disease, that exercise may improve the cognitive function or delay the progression of the disease, but reinforced the need for more studies (Cammisuli et al., 2018), while others suggest that the benefits of physical activity and exercise in both, low and high frequency interventions, are efficient (Jia et al., 2019).

EFFECTS OF PHYSICAL EXERCISE ON EMOTIONAL ASPECTS

The two most common class of psychiatric disorders are anxiety and depression, which have several symptoms involved and also, several types. According to Diagnostic and Statistical Manual of mental Disorders (DSM-V) there are three categories of anxiety: anxiety disorders, obsessive-compulsive and related disorders, and trauma– and stressor–related disorders (Association, 2013). It is classified according to specific symptomatology which can also be visualized in other disorders such as panic attacks, obsessive-compulsive disorder, post-traumatic disorder, generalized anxiety. Recurrent and chronic depression on the other hand, may be featured by a set of symptoms involving cognitive and psychological domains, as cognitive, emotional, somatic and motivational symptoms (Archer et al., 2014; Ménard et al., 2016), moreover, according to DSM-V, there are seven common types of depression, including major depressive disorder, persistent depressive disorder and others (Association, 2013). In this perspective, beyond the social/environmental factors, several biochemical

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mechanisms are involved in mood regulation in humans, as the levels of 25-hydroxyvitamin D, folate and B vitamins, hormones such as cortisol and thyroid hormones, and neurotransmitters, such as dopamine, serotonin, glutamate, GABA, and noreprinephine (Anisman & Zacharko, 1992; Hoogendijk et al., 2008; Lin & Kuo, 2013), serving as important targets in nutritional and pharmacological therapy.

There are some experimental models with rodents that are capable of inducing behaviors similar to those observed in patients with anxiety and depression, as the early maternal separation, social isolation, repetitive induced stress and olfactory bulbectomy (Ménard et al., 2016). In this way, in order to investigate the effects of physical exercise over these conditions in experimental models, some studies demonstrated that treadmill exercise ameliorates cognitive repercussions of early maternal separation in rats (Park et al., 2020) and also minimizes the anxiety-like and depression-like behaviors in rats submitted to a single-prolonged stress protocol (consisting in exposing the animal to stressfull tasks, with some breaks between the tasks) (Patki et al., 2014). Another model of induced stress, the chronic unpredictable mild stress, had its effects minimized by swimming exercise in rats (Liu et al., 2013) and this same physical exercise modality, has also been reported as a strategy to ameliorate the depression-like behavior of rats exposed to glucocorticoids in prenatal period (Liu et al., 2012).

Underlying these functional benefits of physical exercise, the literature has pointed out that the monoamine neurotransmission system might be a strong pathway. A study showed that the voluntary physical exercise in rats activated serotoninergic neurons in dorsal raphe nucleus, but not norepinephrine neurons in locus coeruleus and ventral tegmental dopaminergic neurons (Dremencov et al., 2017). Moreover, voluntary physical exercise also has been associated with neurochemical and behavioral response to stress-induced models in rats (B. N. Greenwood et al., 2003; Moraska & Fleshner, 2001; Soares et al., 1999), showing increased levels of serotonin and noradrenaline in hippocampus of rats (Wang et al., 2013) and increased the mRNA levels of serotonin receptor in dorsal raphe nucleus in stress-induced animals (Benjamin N. Greenwood et al., 2003); increased levels of dopamine in medial prefrontal cortex (Chen et al., 2016). At this point it

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is important to highlight that the frequency and intensity of physical exercise practice seem to affect this monoamine neurotransmition system and cause “central fatigue”, that is featured by the reflexes of monoamines overload (Lin & Kuo, 2013). Some studies that submitted rodents to intense induced physical exercise, had higher levels of serotonin in hypocampus, striatum, hypothalamus and midbrain (Jacobs & Bell, 2004) and caused central fatigue; on the other hand, moderate intensity, although increased the seronotin levels, did not cause functional impairment (Lin & Kuo, 2013).

Furthermore, norepinephrine is also associated with anxiety-like behavior and physical exercise seems to be involved in the up-regulation of galanin in locus coeruleus, which may inhibit neuronal firing and consequent suppression of norepinephrine release (Murray et al., 2010; Sciolino & Holmes, 2012). The modulation of the serotoninergic pathway is much more complex, it has different profiles according to the brain region and physical exercise intensity, however, it follows the same reasoning that intense and prolonged exercise may lead to “central fatigue”, while moderate intensity, may not (Lin & Kuo, 2013).

These biological bases found in pre-clinical investigations may have a translational understanding when we observe the results found in clinical studies. Recent meta-analysis showed that depression is alleviated by physical exercise practice (Dauwan et al., 2016; Josefsson et al., 2014; Kvam et al., 2016; Silveira et al., 2013) and some hypotheses raised to explain these benefits is the modulation of cerebral structures, as reviewed by Gujral et al. (2017) that, in one hand, depression is linked to reduced volume of pre-frontal cortex, hippocampus, striatum and anterior cingulate cortex, and on the other, physical activity may oppose this reduction.

CONCLUSION

In this chapter we were able to show that physical exercise may act by several mechanisms that will reflect on higher functions such as memory, learning and emotions. It is clear that this intervention is an effective tool not only for cardiovascular protection as well described in

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the literature, but also for neuroprotection by the modulation of oxidative stress, neuroinflammation, synaptogenesis, angiogenesis and modulation of neurotransmitters release. Several pre-clinical evidence studies suggest the mechanisms underlying how physical exercise works and moderate intensity seems to be more effective. However, more clinical studies must be conducted to determine what is the most appropriate physical exercise protocol for each clinical goal to design a better clinical intervention based on the patient profile.

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Chapter 5

PHYSICAL EXERCISE/ACTIVITY AND ORAL HEALTH: WHAT ARE THE RELATIONSHIPS?

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ABSTRACT

Physical activity and physical exercise are the main topics involving human motor skills. The definition of physical activity is related to body movements, which demand increased energy expenditure by skeletal muscles compared to baseline levels. On the other hand, exercise is a planned and structured activity that comprises all main physical training variables: volume, intensity, frequency, and type of exercise. Oral health is an indicator of health, well-being, and quality of life. Oral and systemic health are interconnected, and capable of altering physical enforcement and individuals' overall health. Metabolic pathways in exercise provoke different responses in the oral cavity. The oral responses to

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exercise may be associated with periodontal disease changes, tooth loss, oral cancer, malocclusion, dental erosion, dental trauma and changes in salivary flow and pH. Also, occlusal factors can influence physical performance related to proprioception and postural control. Association between physical exercise and inflammatory diseases is not yet clearly understood; however, modulation of immunological markers has been postulated as the primary mechanism involved and immune responses of periodontal health, salivary activity, and function. Periodontitis is one of the most prevalent oral diseases and reaching up to 90% of the population. It is considered an inflammatory disease with a multifactorial aspect leading to damages on dental supporting tissues (gum, cementum, periodontal ligament, and alveolar bone). Knowing that physical exercise is an accessible habit to patients and possibly an adjuvant to oral health and conventional periodontal therapy, the associations between periodontitis and physical activity have been investigated. Studies supported that regular exercise practice reduces periodontitis prevalence when compared to a sedentary lifestyle. Physical exercise has effects on periodontal tissue through: 1 - reduction of inflammatory markers such as IL-1, TNF-a, protein C reactive (cytokines are directly responsible for connective tissue degradation and bone resorption); 2 – an increase of anti-inflammatory cytokines levels, such as IL-10; 3 – an increase of antioxidant enzymes on periodontal tissue like GSH and catalase, and 4 – modulation of advanced glycation end-products on periodontal tissue as well as glucose receptors sensitivity improvement. This chapter will briefly approach the relationship of periodontal diseases in the context of moderate, and also high-performance exercise, showing their perspectives related to periodontal health

Keywords: periodontal disease, periodontitis, physical activity, exercise, sports

INTRODUCTION

A definition of oral health is a comfortable and functional relationship between oral components that allows individuals to continue their desired social role. Oral health is characterized by the World Health Organization (WHO) as an essential indicator of health, well-being, and quality of life. This term comprises a variety of

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disorders, diseases, and conditions that include dental caries, periodontal disease, tooth loss, oral cancer, oral manifestations of HIV infection, oro-dental trauma, and congenital disabilities, such as cleft lip and palate (WHO, 2017).

Therefore, it is necessary to understand the health-disease processes that involve the mouth through two levels of analysis: one related to the reciprocal interactions that oral diseases have with other systemic diseases, and another, a personal level, evaluating the aspects of the individual well-being compromised by the presence of oral diseases (Preshaw et al., 2012). In this way, physical activity and exercise can be applied to promote oral health maintenance (Ferreira et al., 2019). Oral health is completely linked to systemic health, then exercise and physical activity may be capable of modulating responses in the stomatognathic system (Merchant et al., 2003; Sakki et al., 1995). As the body works as a chain of interconnected interactions, oral health may also be capable of altering physical performance and an individual's overall health, defining the whole process as a two-way one (Needleman et al., 2013).

PHYSICAL EXERCISE AND SYSTEMIC HEALTH

Physical activity and exercise are important tools for health maintenance, being related to changes in systemic aspects. Thus, several studies seek to apply their relation with oral health (Ferreira et al., 2019). An essential factor to be highlighted is the characteristics of the exercise. Its intensity and duration are associated with the activation of different metabolic pathways that consequently provoke different responses, not only in a systemic perspective, but also in the oral cavity.

Physical inactivity can increase disease risk factors when interacts with other individual characteristics (age, diet, gender, genetics) (Ruegsegger & Booth, 2018). The emerging evidences show the role of physical activity in modulating the cardiorespiratory, neuromuscular, and metabolic systems. In the cardiorespiratory system, the maximal oxygen consumption during exercise (VO_2max) reflects the cardiovascular, respiratory, and neuromuscular systems work. The

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increase in $\dot{V}O_2max$ is directly associated with a reduced risk of multiple comorbidities (Gries et al., 2018). In the neuromuscular system, exercise practice enhances the metabolic potential of muscles through an increase of oxidative capacity and insulin sensitivity. Moreover, physical exercise can also alter neuronal functional and structural plasticity mechanisms involved with the improvement of memory, cognitive performance, functional brain responses, and motor skills (Bangsbo et al., 2019; Harridge & Lazarus, 2017).

The benefits of physical exercise in cardiovascular and neuromuscular systems are associated with metabolic functions. Exercise activates an up-regulation insulin-signaling metabolic pathway, reducing glucose and attenuating type-2 diabetes (Ruegsegger & Booth, 2018). Like other body systems, the stomatognathic system undergoes changes induced by the practice of physical exercise. Good oral hygiene, combined with regular exercise, can protectively and beneficially change the oral cavity to health maintenance. The improvement of oral health can occur through several mechanisms: changes in the oral microbiota by decreasing the periodontopathogenic bacteria or modification in the salivary composition, flow, viscosity, and pH (Pan et al., 2019). When altered by poor oral health and affected by oral diseases, total physical performance and fitness may be impaired (Bramantoro et al., 2020). Also, exercise has an intertwined relationship with postural proprioception and occlusion (Bramantoro et al., 2020).

In this way, in the next pages of the chapter, we will address the primary evidence of physical exercise benefits in three important aspects for maintaining oral health: occlusion, periodontal health, and salivary function.

Dental Occlusion and Physical Performance

Dental occlusion is characterized as a static relationship of tooth contacts (Franco et al., 2012; Ricketts, 1969). Besides that, these contacts between the maxillary and mandibular teeth can influence the stomatognathic system dynamic processes, such as chewing (Franco et al., 2012) – which in altered occlusion it is called malocclusion. It's

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currently debated that the presence of this craniofacial condition may be associated with poor physical fitness (Bramantoro et al., 2020). This is due to the physical performance dependency on several variables. One of these variables is the posture that, when correct, allows the individual to use the neuromuscular potential (Angelozzi et al., 2008; Julià-Sánchez et al., 2020; Militi et al., 2020).

Postural control is one of the bases to attain optimal physical performance. By contrast, the evidences point out that poor balance control induces a higher risk of injury during exercise (Hrysomallis, 2007; Julià-Sánchez et al., 2020). Ideally, the human body has four parts aligned in one plane: the most posterior region of the head, shoulder blade, buttocks, and heels (Julià-Sánchez et al., 2020). A deviation in this alignment results in the loss of verticality resulting in muscle compensations that can affect the entire musculoskeletal system (Julià-Sánchez et al., 2020; Militi et al., 2020). Based on this, the disturbance in occlusion may be influenced by the postural control and body balance after a long period of changed neural integration (Leroux et al., 2018; Militi et al., 2020). Besides, it has been argued that dental occlusion can differentially contribute to postural control depending on external disorders, with a more significant association with postural control when aggravating conditions are present (e.g.., unstable conditions and muscle fatigue) (Bergamini et al., 2008; Julià-Sánchez et al., 2020; Julià-Sánchez et al., 2015; Julià-Sánchez et al., 2016).

In this sense, malocclusion can also alter muscle function while swallowing - one of the factors associates with crackling - limited mouth opening and ear pain, strongly related to temporomandibular joint (TMJ) (Militi et al., 2020). There is a sensory nerve transmission directed to the cerebral cortex that, in the presence of dental malocclusion, induces motor nerve transmissions that will alter the muscular structure, causing pain in different anatomical areas distant from the stomatognathic system (Angelozzi et al., 2008; Bron et al., 2012). In this way, it still affects other body areas and causes headache, pain in arms and neck, or even disorders in the feet, resulting in limitation of physical performance (Angelozzi et al., 2008; Militi et al., 2020).

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Thus, it is evident that occlusal factors can influence physical performance, thus making oral health applications relevant in sports and the science of exercise, mainly with dental occlusion related to proprioception and postural control, being able to prevent sports injuries.

Saliva and Physical Exercise

Saliva is a biological fluid that works as the body first defense to ingested pathogens. It moistens the oral cavity soft and hard tissues, playing an essential role in maintaining oral health through the hydration, lubrication of oral tissues, dental remineralization, digestion, and pathogen exclusion (Ligtenberg et al., 2015). In addition, it acts as a biomarker used to indicate the biological state to determine physiological or pathological processes (Palacios et al., 2015).

Saliva represents a widely used clinical tool to evaluate biomarkers in sports areas in order to analyze the effects of exercise on different systems (Souza et al., 2019). Saliva is also used to assess the rate of fitness, muscle damage, hydration/dehydration system, oxidative damage, and fatigue (Palacios et al., 2015). Besides that, saliva samples can be analyzed and show the presence and/or levels of steroids, peptides, and immune markers in exercise (Papacosta et al., 2011).

Physiologically, saliva secretion is modulated by the autonomic nervous system, with sympathetic signaling resulting in protein secretion, while parasympathetic signaling results in mucin and water secretion. During physical exercise, sympathetic activation predominates (Papacosta et al., 2011). This signaling can increase the secretion of protein expression from salivary glands. However, there is a wide individual variation between salivary composition and salivary glands, which respond to different stimuli, including the practice of physical exercise (Sant'Anna et al., 2019).

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Exercise might induce changes in several salivary immunological components, such as immunoglobulins, endocrinological status through cortisol and testosterone hormones, endothelial function through nitric oxide levels, and exercise intensity such as lactate, proteins, amylase activity, and electrolytes (Chicharro et al., 1998; Palacios et al., 2015).

It is known that physical exercise can influence salivary flow rate and composition caused by panting and dehydration (Mulic et al., 2012). Since physical exercise elicits increased sympathetic activation causing marked vasoconstriction and parasympathetic withdrawal, it is expected that exercise could reduce saliva flow rate and volume. The lower secretion of saliva can cause sympathetic nerve activation, dehydration, hyperventilation, and high-volume airflow in high intensity exercise, changing physical fitness (Mulic et al., 2012; Needleman et al., 2014; Papacosta et al., 2011). The lower salivary flow rate can lead to a decline in oral irrigation function, dry mouth, and a reduction in protective properties of saliva against dental plaque biofilm, being susceptible to the onset of dental caries, dental erosion, and periodontal disease (Needleman et al., 2013; Tanabe-Ikegawa et al., 2018)

Moreover, the decrease in salivary pH and flow rate might be associated with dental erosive lesions (Frese et al., 2015; Mulic et al., 2012). The significant increase of saliva pH at maximum workload suggests a compensatory reaction to saliva imbalance. Exercise can alter the composition of saliva, leading to an increase of proteins and metabolites with antioxidant function and a temporary increase of saliva viscosity right after exercise (Frese et al., 2015; Ligtenberg et al., 2015).

Exercise is associated with the up- and down-regulation of steroid hormones, such as cortisol, testosterone, progesterone, and aldosterone. The relationship between saliva and steroid hormone levels during exercise can be used as a diagnostic and clinical tool for training conditions appraisal (Frese et al., 2015; Gatti et al., 2011). The stress pathways also modulate immune responses with the increase in the circulating stress hormones, as catecholamines and cortisol in response to exercise (Rutherfurd-Markwick et al., 2017). The salivary cortisol rate increases linearly with exercise intensity. A hormonal adaptation characterizes this response to lower levels of cortisol in

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exercise. Therefore, exercise-related hormonal response is a useful indicator of overtraining (Chicharro et al., 1998; Papacosta et al., 2011).

In the analysis of salivary immunological compounds, immunoglobulin IgA, the best indicator of mucosal immunity, provides a potential defense against pathogen on the mucosal surfaces, decreasing salivary IgA levels in an exercise-dependent trend. The reduced concentrations of salivary IgA may allow for increased pathogens in the oral mucosa. Besides, some studies show that lower concentration and secretion of IgA are associated with increased salivary cortisol levels, which indicate that higher levels of cortisol may be a precursor for mucosal immunity suppression (D'Ercole et al., 2016; Papacosta et al., 2011; Sari-Sarraf et al., 2007).

Also, the practice of exercise can activate salivary enzymes and protein modulation increasing β-adrenergic signaling (Sant'Anna et al., 2019). Salivary alpha-amylase is used as a biomarker of exercise intensity due to its correlation with the lactate threshold (Sant'Anna et al., 2019). In addition to oral enzymes activity, the quantification of salivary β -galactosidases activity is considered a method for halitosis evaluation. Exercise practice showed a significant decrease in salivary β-galactosidases level, halitosis, tongue coating index, and gingivitis (Petrini et al., 2018).

Similarly, salivary protein concentration can indicate an anaerobic level since it correlates with lactate blood in the physical effort (Palacios et al., 2015). A recent study showed that increased concentrations of cystatin C and cystatins type S were observed in saliva in response to both aerobic and anaerobic exercise, associated with near maximal effort. It was observed that an increase in salivary amylase levels, as well as plasma lactate, was consistent with exercise; the time of recovery for cystatin was faster than the one for amylase, implying a different secretory system (Sant'Anna et al., 2019).

Therefore, it is observed that the salivary modulation caused by the practice of physical exercise mentioned above can modulate the conditions of oral health and physical performance.

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Physical Activity, Exercise and Periodontal disease

If practiced regularly, physical activity and exercise can increase various physical capacities such as cognition (Fernandes et al., 2018), cardiovascular physiology, weight control (de Souza et al., 2018) and prevention of other systemic diseases. When considering the interaction between physical exercise and systemic diseases, especially inflammatory disorders, there are still points that are not fully understood; however, an immunological change pattern has been postulated as a link between those conditions (Gleeson et al., 2011)

Exercise has been linked to changes in inflammatory markers, including a reduction in C-reactive protein levels (a systemic inflammation marker) (Fernandes et al., 2018; Malali et al., 2010) and modulation of interleukins (pro and anti-inflammatory), such as IL-1, IL-6, and IL-10. Changes in these proteins expression are associated with several diseases, including periodontal disease (Beck et al., 2018).

Periodontal disease is an oral inflammatory condition leading to damage in dental supporting tissues: gum, periodontal ligament, cementum, and alveolar bone (Murakami et al., 2018). Dental follow-ups, oral hygiene methods, and self-care measures are needed to achieve periodontal health. However, several issues like individual host-responsiveness, oral microbiota, and chronic diseases may vary among individuals and modify periodontal disease progression (Lang & Bartold, 2018). Moreover, periodontal diseases worsening is linked to a low-level systemic inflammation that affects different diseases in a possible reciprocal mechanism (Ferreira et al., 2019; Potempa et al., 2017; Teixeira et al., 2017).

Additional procedures to improve professional and personal care can lead to possible adjuvant therapies for periodontitis. Thus, as it induces physiological and biochemical changes, physical exercise can also be seen as a non-pharmacological intervention for the treatment of disorders related to aspects associated with damages to the dental supporting tissue (Ferreira et al., 2019; Lang & Bartold, 2018).

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Periodontal Disease Definition

Periodontal disease is a multifactorial condition with a significant inflammatory profile resulting from the interaction among bacterial pathogens, host response, genetic factors, environmental factors, and individual health habits (Chapple et al., 2018). According to the latest American Academy of Periodontology and European Federation of Periodontology workshop, periodontal diseases have subdivisions that cover the extent and involvement of different structures that constitute the periodontium, such as gingivitis and periodontitis (Caton et al., 2018).

Gingivitis signs and symptoms, such as bleeding while flossing, halitosis, and swelling, are related to superficial tissues such as the marginal gum. When damage comprises deeper tissues, periodontitis is present, and other clinical signs must appear, such as gingival bleeding, gingival recession, dental mobility, destruction of the periodontal ligament, alveolar bone resorption, and, ultimately, tooth loss (Papapanou et al., 2018) (Figure 1).

As a primary etiological factor, microbial biofilms, mainly gram-negative bacteria, are the main contributors to periodontal disease development. However, periodontal disease progression also depends on factors non-related to biofilms, such as the host immune response, genetic factors, and environmental factors (habits and lifestyle) (Gallagher et al., 2019). Nevertheless, some studies related to physical activity (environmental factor related to lifestyle) report the possible relationship between physical exercise that may reduce the prevalence of periodontal disease (Al-Zahrani et al., 2005; Ferreira et al., 2019; Merchant et al., 2003).

The pathogenesis of periodontal disease consists, in summary, in a microbial challenge against host immune response. Antigens, carbohydrates, and proteins related to the bacterial cell wall (e.g., lipopolysaccharides - LPS) undergoes the reaction of polymorphonuclear leukocytes (PMNs) and the complement system. It is noteworthy that even in a clinical health situation, the microbial challenge is present symbiotically with the oral environment. In this situation, dental plaque levels are controlled by brushing and flossing

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methods, which results in a proportional immune response in periodontal tissues(Cekici et al., 2014).

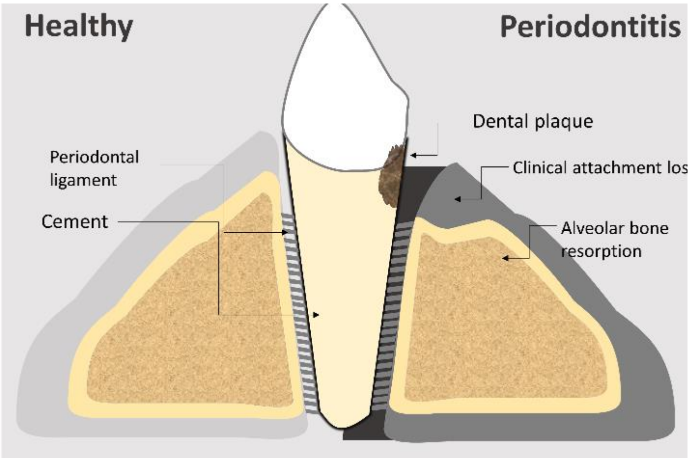

Figure 1. Periodontal tissue representation and periodontal status regarding health and inflammation aspects. Clinical attachment loss (CAL) and alveolar bone resorption clinically defines a periodontitis status.

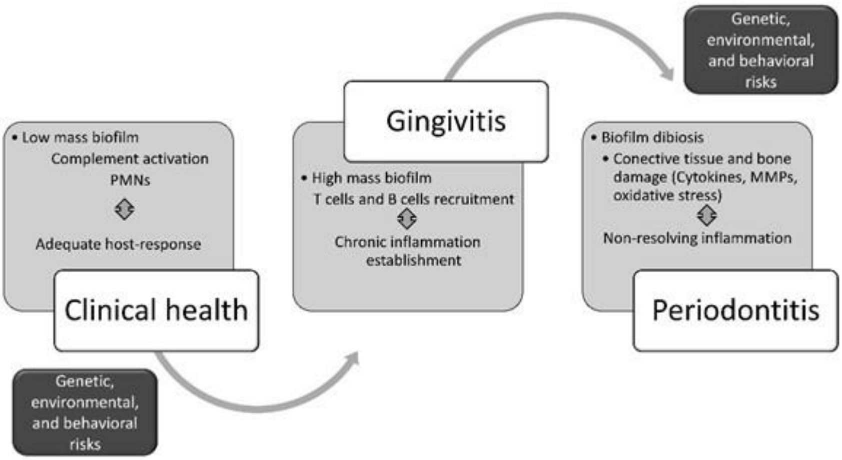

Figure 2. Periodontal disease pathogenesis. Three stages are considered to establish the progression of periodontitis. Abbreviations: MMPs, matrix metalloproteinases; PMNs, polymorphonuclear neutrophils.

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With the absence of dental plaque removal through hygiene methods, the inflammation is set with gingivitis and its characteristic signs and symptoms. From 7 to 14 days, the biofilm virulence results in the recruitment of a high number of PMNs and T and B lymphocytes to the infection site (Meyle & Chapple, 2015). If the biofilm remains after 21 days, specific periodontal pathogens proliferation tends to increase and develop a deeper inflammation of the supporting tissues. Antibodies, plasmocytes, PMNs are the main subjects found at this stage and responsible for the release of metalloproteinases (MMP-2 and MMP-9), reactive oxygen species, prostaglandins, cytokines (IL-1beta, IL-6, TNF-alpha, protein C reactive) in dental supporting tissues (Cekici et al., 2014; Sanders et al., 2009). Consequently, there is a degradation of periodontal tissues resulting in clinical attachment loss (periodontal tissue detachment and alveolar bone resorption), the main difference between gingivitis and periodontitis. These microbial biofilm effects can develop more slowly or more quickly depending on factors that modulate the inflammatory response, such as genetic and epigenetic, environmental, and behavioral factors. Figure 2 presents a representation model of periodontal disease pathogenesis and its central modulators (Meyle & Chapple, 2015).

Periodontal Disease and Systemic Inflammation

Periodontal disease has a strong influence on several systemic conditions, whether genetic or acquired origin. Among the commonly known systemic diseases, diabetes is reported as a modifying factor for periodontal disease (Preshaw et al., 2012). Patients with high glycemic levels are two to six times more likely to progress to severe periodontitis (Tsai et al., 2002). Thus, the treatment involves interconnected aspects to the general health situation of the patients involving several health professionals, such as physicians, dentists, nutritionists, trainers, among others.

Other systemic diseases that are commonly related to an inflammatory profile and have recently been linked with periodontitis are cardiovascular diseases (Lockhart et al., 2012). Cardiovascular diseases are recognized as the leading cause of death, covering 30%

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of all deaths worldwide. According to the ninth review of the international classification of diseases, cardiovascular diseases are 1 - ischemic heart disease, 2 - cerebrovascular diseases, and 3 - vascular diseases of arteries, arterioles, capillaries (also known as peripheral vascular diseases). Such conditions consist of a long inflammatory process characterized by acute episodes such as myocardial infarction and stroke (Lockhart et al., 2012).

Potential relationships between periodontitis and cardiovascular diseases involve direct and indirect mechanisms between both disorders. Among the direct mechanisms, bacteremia with resulting vascular infection is one of the hypotheses of association. More than 200 species are reported in the oral cavity, and bacteremia is a process that commonly occurs in chewing and brushing, especially in cases of periodontitis (Lockhart et al., 2012). Periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerela forsythia,* and *Prevotella intermedia* are related to a possible endothelial vascular infection and affect the formation of atheroma (Almeida et al., 2018).

Among the indirect mechanisms, the systemic inflammation perpetuated by inflammatory mediators of periodontitis is associated with acute myocardial infarction, ischemic stroke, and increased thickness of the carotid tunica intima. The inflammatory markers in question are C-reactive protein, IL-1β, IL-6, IL-8, TNF-α, which are present in periodontal disease and are responsible for the inflammatory response that will promote the loss of insertion periodontal tissues (Malali et al., 2010; Toker et al., 2018). Thus, in addition to the standard treatment for periodontitis, measures that make it possible to reduce the risk for systemic inflammation are recommended to prevent progression or relapse (Lang & Bartold, 2018).

Among the treatments for periodontal disease, mechanical debridement of biofilm on dental surfaces, monitoring possible systemic changes, and changing habits related to oral hygiene are crucial elements in reducing clinical signs and symptoms, as well as maintaining health status (Heitz-Mayfield & Lang, 2013). When relating systemic diseases to periodontitis, other concomitant treatments must be associated with controlling the loss of insertion of dental supporting

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tissues (Lang & Bartold, 2018). Thus, physical activity and exercise can be a preventive measure option.

EXERCISE AND PERIODONTAL DISEASE ASSOCIATIONS

As a planned and structured activity, physical exercise enables the improvement of physical capacities related to different systems. Also, physical exercise has been suggested as a preventive and therapeutic method in the treatment of various pathophysiological conditions, such as cardiovascular issues (Warburton & Bredin, 2017) and, more recently, periodontal disease (Ferreira et al., 2019). Knowing that physical exercise aims to improve physiological capabilities to bring benefits to individuals, several studies with different exercise qualifications (aerobic or anaerobic) such as swimming, acrobatic or voluntary exercise, running on a treadmill, among others, as well as high and low intensity, intermittent or continuous, of short or long duration, have been developed in animals, to simulate human physical activity (Arida et al., 2007).

Instead of a sedentary lifestyle associated with numerous pathologies, physical exercise has been of great importance to combat diseases such as obesity, hypertension, diabetes, osteoporosis, and immunosuppression, among others (Garber et al., 2011). Another essential exercise intervention for health is the prevention or improvement of brain function in neurodegenerative diseases such as Parkinson and Alzheimer (Chen et al., 2016; R. M. Fernandes et al., 2018). Regular exercise practice reduces the risk of several metabolic diseases due to their anti-inflammatory effects (Gleeson et al., 2011). However, although physical exercise has a protective effect against various diseases, the practice is also associated with cellular and tissue damage caused by the excessive production of reactive oxygen species (de Souza et al., 2018).

It is important to note that reactive oxygen species during physical exercise can be produced by different mechanisms such as oxygen alterations in mitochondria, inflammatory process, ischemia and reperfusion processes (Powers & Jackson, 2008). Although there is a relationship between the effects of exercise and the formation of free

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radicals, there are indications that the cellular environment increases the endogenous concentration of antioxidants to compensate for the stress caused by physical activity (R. A. Fernandes et al., 2018; Powers et al., 2016).

Studies suggest that physical exercise can cause an antioxidant system adaptation, with an increase in regulatory enzymes, providing an increase in resistance against stress and, consequently, reduction of oxidative damage (Sallam & Laher, 2016). Therefore, although controversial points regarding the protective mechanisms resulting from physical exercise and reactive oxygen species production modulation, it was found that cellular and tissue damage by free radicals occurs in aerobic and anaerobic physical activities, especially in high-intensity efforts (Powers & Jackson, 2008). However, evidence shows that different results may occur due to the heterogeneity of applied methods.

Periodontal disease and diabetes have an established bidirectional relationship (Preshaw et al., 2012). Poor glycemic control (>7% Hb1ac) leads to unbalance of inflammatory biomarkers, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (Preshaw et al., 2012). In this line, an increase of reactive oxygen species and advanced glycation end products (AGEs) in the periodontal tissues also increases inflammation in the periodontium of people with high glucose levels (Casanova et al., 2015; Chapple & Matthews, 2007). Knowing that physical exercise is accessible to patients, and possibly an adjuvant strategy to conventional periodontal therapy, the associations between periodontitis and physical exercise have been investigated approaching glucose level modulation. Among the research lines, this activity has effects on several organ systems, and some authors suggest an association between the increased sensitivity of insulin receptors to glucose (Beck et al., 2018; Garber et al., 2011) which has repercussions for periodontal disease reduction since high glucose levels aggravate the clinical condition of periodontal disease.

Physical exercise also shows a modulating effect on cytokine levels, especially in pro-inflammatory cytokines (tumor necrosis factor - TNFα, interleukin 1a - IL-1a, interleukin 1b - IL1 -b, interleukin 6 - IL6) (Sanders et al., 2009). It is already known that interleukin 1 beta (IL-1β) is a pro-inflammatory cytokine directly related to inflammatory levels of

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periodontitis and other diseases (Almeida et al., 2018; Sanders et al., 2009). Regular exercise has been associated with lower levels of IL-1β, IL-6, IL-8, and TNFα (Hajizadeh Maleki et al., 2018). Besides, the prevalence of periodontitis comparing patients who practiced regular physical activity and sedentary patients (Sanders et al., 2009) was also reduced when cytokine levels suffered effects from periodontal treatment and exercise. However, baseline cytokines levels may return if the activity is not regularly practiced (Hajizadeh Maleki et al., 2018). Then, authors suggested that physical activity may practice regularly

It is noteworthy that exercise is also related to IL-10, a cytokine responsible for reducing pro-inflammatory cytokines expression (Albuquerque et al., 2012; Cekici et al., 2014). Muscle contraction induces a significant increase in the synthesis of IL-10 through intracellular calcium ion increase made by IL-6 stimulation (Conroy et al., 2016). Periodontitis has been associated with a low-grade systemic inflammation leading to imbalances in cytokine levels (D'Aiuto et al., 2010), and IL-10 has low levels in individuals with periodontitis (Albuquerque et al., 2012). Reductions of IL-10 are associated with severe cases of periodontitis, and also some IL-10 polymorphisms have been related to periodontal disease susceptibility (Yang & Huang, 2019). Thus, physical activity and exercise may play a role in cytokine imbalance related to periodontitis and possibly working for prevalence reduction (Conroy et al., 2016; Ferreira et al., 2019)

Another possible relationship between physical exercise and periodontal disease is the alteration of oxidative stress markers (Aboodi, 2015; D'Aiuto et al., 2010). Studies carried out in patients with an active lifestyle point to an increase in reducing enzymes such as GSH, SOD, and catalase, known to be antioxidant markers that work directly in the reductions of NAPH and hydrogen peroxide (Anna et al., 2016; Rodrigues de Araujo et al., 2018). However, the methods vary between studies and, consequently, the results are still heterogeneous as to the association of physical exercise in reducing oxidative stress produced by periodontal disease.

To better understand the mechanisms that exercise influences on the course of periodontal disease, studies in humans and animals have evaluated serum concentrations of bone biomarkers before and after physical activity. The main researched biomarkers are the triad

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osteoprotegerin (OPG)/receptor activator of NF-κB (RANK)/RANK ligand (RANKL), and the cytokines tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) (Andrade et al., 2018; Kim et al., 2019; Kwan Tat et al., 2004).

The role of RANKL in bone physiology is the stimulation of osteoclastic differentiation and the inhibition of osteoclast apoptosis (Cekici et al., 2014). Regarding OPG, its biological effects on bone cells include the inhibition of terminal stages of osteoclast differentiation, suppression of mature osteoclast activation, and induction of apoptosis. It represents an antagonist receptor that neutralizes the biological effects of RANKL, acting as an inhibitor of bone resorption (Cekici et al., 2014). Besides, OPG can directly inhibit osteoclast activity, without depending on RANKL, through interactions with some receptors present on osteoclast (Kwan Tat et al., 2004).

OPG synthesis is induced and stimulated by TNF-α, IL-1, hormones (vitamin D, estrogen, and glucocorticoids), and mesenchymal transcription factors, whereas parathyroid hormone and prostaglandin E2 (PGE2), suppress its production (Kwan Tat et al., 2004). The role of TNF-α and IL-6 is to induce the differentiation of osteoclastic progenitors into osteoclasts through the passage of prostaglandin E2 (PGE2) in bone tissue and the increase of the secretion of RANKL on the osteoblasts surface (Kim et al., 2019). During inflammatory diseases, TNF-α and IL-1 play an essential role once they induce the expression of many other pro-inflammatory molecules and hematopoietic cytokines as IL-6 (Tobeiha et al., 2020).

Therefore, considering that many studies have shown a reduction in the prevalence of the periodontal disease in groups with physical exercise, along with the several advantages of training in protecting bone remodeling, it was expected that there would be changes in bone activity biomarkers, with a decrease in RANKL and an increase in OPG, depending on the distance and duration of the activity (De Oliveira Ferreira et al. 2019; Andrade et al. 2018; Tobeiha et al. 2020). For example, a study found this result during a long-distance run, which represents an extreme situation for the human skeleton under stress conditions. That increased OPG/RANKL ratio may be due to the hormonal regulation caused by the exercise stress or even the mechanical strain of running. A constant increase in OPG levels

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through regular exercise can lead to a decrease in RANKL and, consequently, a more prolonged inactivation of osteoclasts, resulting in a reduction in bone resorption in the face of periodontal disease (Ziegler et al., 2005).

Another study reported that even though cycling is a low-impact activity, it could stimulate a response in bone alkaline phosphatase BAP, OPG, and RANKL. The former increased 5 min after cycling, which may be caused by the small mechanical strain on the bone associated with that activity. OPG and RANKL also increased significantly 5 min after exercise, which may be explained by the increase of IL-1, TNF-α, and IL-6 (Hajizadeh Maleki et al., 2018; Mezil et al., 2015). Many reasons can explain the higher levels of IL-6: local muscle production because of muscle contractions; elevations in IL-1 and TNF-α that act on muscle due to damage caused by eccentric contractions; and by the liver and adipose tissue (Ferreira et al., 2019). The stimulation of IL-6 by IL-1 and TNF-α leads to the positive regulation of its antagonistic receptors and soluble TNF- α receptors, which increase immediately after IL-6 to act as a negative feedback mechanism for the pro-inflammatory effects of IL-1 and TNF-α (Mezil et al., 2015).

However, many clinical studies have reported that exercise alone was not able to change the levels of bone markers, such as RANK/RANKL and OPG, but it generally reduces the levels of cytokines reabsorbed by bones such as TNF-α and IL-6 (Kim et al., 2019; Marques et al., 2013).

Thus, since a considerable increase in these bone biomarkers occurs in periodontal disease, exercise alone may not attenuate the damage caused by alveolar bone loss and should be combined with a change in oral hygiene habits and clinical periodontal treatment.

Periodontal Disease and High-Performance Exercises

When analyzing the relationship between exercise and periodontal disease, professionals must consider that the systemic influence of both can occur with dual-path mechanisms, especially when we find

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that periodontal disease has been reported with systemic impact. Thus, when differentiating the populations analyzed, whether sedentary, regular physical activity practitioners, or athletes, the physiology applied to exercise and the pathogenesis of periodontal disease will interconnect in a complex way inherent to the individuality of exercise analysis and periodontitis.

Some studies indicate that oral health and the effects on athletes performance have a positive association (Gay-Escoda et al., 2011, Solleveld, Goedhart, and Vanden, 2015). Unlike the beneficial effects of physical activity on periodontal disease, a relationship in which periodontal disease is detrimental to performance was observed when the population studied is elite athletes. A cross-sectional study evaluating Olympic athletes' attendance in a specific polyclinic for competitions identified that 30% of all consultations were related to dental causes, second only to osteomioarticular causes (Vanhegan et al., 2013). In this perspective, the relationship between periodontal disease and exercise is also established in cases where performance is a priority for competitions.

A cross-sectional study involving 278 Olympic athletes reported that poor oral health (absence of teeth and cavities, mainly) negatively impacted the athletes perception of the quality of life, training, and performance. In this same study, the periodontal evaluation of the athletes indicated a high prevalence of the periodontal disease, with 75% of the athletes presenting gingivitis cases and 15% of periodontitis. When the perception of the effect of oral disease on the athlete’s performance was analyzed, there was no relationship between periodontal disease and the understanding of athletes about the impact on performance, even though it was quite prevalent.

Another study evaluating the effects of oral health on the performance of soccer athletes reported associations between the indexes of plaque and depth of probing, indices often used in the evaluation of oral hygiene, and periodontitis, with the occurrence of muscle injuries (Gay-Escoda et al. 2011). Other authors also sought to verify the relationship between oral diseases and the appearance of injuries by assessing 215 professional soccer athletes. About 43% reported one oral health problem and 20% two or more oral health problems, including periodontal disease (Solleveld, Goedhart, and

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Vanden Bossche 2015). In the multivariate analysis, the presence of one or more issues related to oral health was associated with all types of injuries assessed by the group, such as repeated exercise-associated muscle cramps, muscle or tendon reinjury, and multiple kinds of reinjury.

Still, regarding the effects on performance perception by the athletes, we can consider the hypothesis possibly related to the little symptomatic picture of periodontal disease (Lang & Bartold, 2018). Most of the cases present an absence of pain in the gingival tissue. Symptoms in mild and moderate cases of periodontal disease may be restricted to gingival bleeding during brushing or flossing (Oppermann et al., 2015). Still, another problem related to patients' self-perception is that gingival bleeding in periodontitis cases is not clearly evident and can even be masked by smoking or by the presence of comorbidities such as diabetes. In severe cases, symptoms include dental mobility, increased spaces, and tooth loss without the intervention of a dentist (Papapanou et al., 2018). Thus, further studies are needed to demonstrate the effects of periodontal disease on athletes performance using questionnaires similar to a well-validated proposed by CDC and the American Academy of Periodontology (Abbood et al., 2016; Reiniger et al., 2020) or using methods that evaluate the effects of a periodontal treatment program associated with the evaluation of parameters related to the training and performance of athletes.

Possible mechanisms of interaction between periodontal disease and athletic performance are related to the multifactorial pathogenesis of periodontal diseases (Meyle & Chapple, 2015). Athletes are regularly subjected to stress and anxiety due to the demands of their activity. Hormonal changes are constant in situations of psychological need, which are an aggravating factor of periodontal disease, as they affect self-care and create environments conducive to biofilm in addition to systemically modulation of the host inflammatory response (Gallagher et al., 2019). If the periodontal disease worsens, systemic changes in IL-1 and IL-6 may be related to a higher risk of developing muscle fatigue and, consequently, reinjuries (Solleveld et al., 2015). Little salivation and production of crevicular gingival fluid are related to exercise also proposed as a possible risk factor since saliva participates in innate immunity in preventing dental plaque adhesion

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and, in turn, damage to periodontal tissues. In this way, a reciprocal interaction in these cases is possible.

There is still some difficulty in exposing substantial evidence for these interactions in athletic performance within all those as mentioned earlier. Methodological problems related to the studies, such as small sample size considering elite athletes, absence of a control group in studies, and heterogeneity in periodontal or exercise evaluation, make it challenging to present the existing relationships in both conditions. Also, the need for prospective studies to assess more accurately the effects, incidence, and related risk factors is vital for position stands.

Even with several methodological challenges presented in the studies, a recent consensus statement of the effect of oral diseases on athletic performance established some critical points in the health care of athletes and that can guide the conduct of doctors, dentists, coaches, physiotherapists, sports federations, and others (Needleman et al. 2014):

- *Oral health*: Poor oral hygiene is common in elite athletes. Oral health is a fundamental right of athletes but has consistently been miserable with a high treatment need. Dental caries, dental erosion, periodontal disease, and pericoronitis (infection around impacted teeth) are the primary oral health conditions affecting athletes. Dental trauma in 'at-risk' sports is also recognized. The effect of poor oral health on athletes may have both short-term and long-term consequences. In short, poor oral health can cause pain and distress, difficulties in eating and sleeping, reduced quality of life, and performance impact. The long-term consequences include increased risk of tooth loss, increased treatment needs, and resulting functional and psychological impairments.
- *Causes of poor oral health:* There are many challenges to the oral health of elite athletes, some of which act at the level of the athlete and others within the peer, community, and sport organizational level. These issues include nutritional challenges from frequent carbohydrate intake and acidic sports drinks, impairment of host responses due to dehydration, mouth drying and intensive training, poor health behaviors and oral health

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literacy, and lack of adequate health promotion/ preventive support.

- *Impact on performance*: Emerging athlete self-reported evidence suggests that poor oral health negatively affects athletes' training and performance. The mechanisms behind this effect might include pain, reduced well-being and quality of life, and increased systemic inflammation.
- *Improving and maintaining the oral health of athletes:* Oral diseases are preventable with well-characterized interventions at a low cost. Some responses are more dependent on behavioral change and adherence to care than others. To achieve a sustained effect, oral health should be embedded within other health promotion aspects, taking into account the structural issues and inter-relationship of athletes within their sport and peer networks. Such an approach could also achieve mutual benefits for general health, well-being, and performance. Regular assessments of oral health by a dental professional, especially preseason, will allow for personalization of prevention plans and early treatment of any disease. National sports funders and policy organizations should take the lead in integrating such an approach. Mitigation of risk approaches should also be investigated as part of an oral health strategy.
- *Research and surveillance*: The research base to inform sport and exercise medicine is limited in amount and quality.

CONCLUSION

Based on available research, this chapter alluded that regularly (3-5 days/week) moderate physical activity and moderate exercise provide benefits that may affect the inflammatory response of individuals reducing the risk of systemic inflammatory disorders. Other comorbidities such as cardiovascular diseases and high glucose levels were also preventable with a regular practice of exercise affecting the dental supporting tissues proportionally. Regarding the aspects that involves high-performance or high-intensity exercise, care related to

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oral hygiene and to maintaining the health of athletes must be part of health services attention, since high performance exercise is also associated with low perception of quality of life, injuries, and oral diseases. Thus, health is established with good dental care, and better results may be achieved during competitions.

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Chapter 6

EXERCISE: PHYSICAL, PHYSIOLOGICAL AND PSYCHOLOGICAL BENEFITS ON RHEUMATIC INFLAMMATORY DISEASES

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ABSTRACT

Immune-mediated inflammatory rheumatic diseases (IMRD) comprise a group of heterogeneous and pleomorphic chronic inflammatory diseases that can affect different organs and systems. Several studies have already shown a higher prevalence of traditional cardiovascular risk factors in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and

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spondyloarthritis (SpA). In the same context, chronic inflammation and immune alteration underlying Sjögren's syndrome (SSj) and inflammatory idiopatic myopathies (IIM) are also reported to be associated with augmented risk of atherosclerosis and increased frequency of cardiovascular disease. However, the increased cardiovascular risk in these diseases are not only due to these factors, suggesting that diseases per se play an important role in the development of early atherosclerotic disease, an important cause of morbidity and mortality. In addition, these patients may have fatigue, depression, worse quality of life, and lower tolerance to exercise, aerobic capacity and physical activity level than sex and age-paired healthy individuals. On the other hand, the practice of regular physical exercise has been described as a useful and beneficial modality in reducing cardiovascular morbidity and mortality in the general population, increasing life expectancy and decreasing cardiovascular outcomes, as well as improving fatigue, aerobic capacity, quality of life and depression. Although the practice of regular physical exercise presents multiple benefits for patients with IMRD and is a useful and inexpensive strategy that can be combined with the pharmacological treatment of the diseases, few patients perform regular physical exercise. Physician should be stimulated to encourage patients to perform exercise regularly. This chapter aims to describe the main scientific evidence in the practice of physical exercise in patients with SLE, RA, SpA, IIM and SSj.

Keywords: systemic lupus erythematosus, rheumatoid arthritis, spondyloarthritis, Sjögren syndrome, exercise, cardiovascular diseases, non-pharmacological therapy

1. Introduction

There are currently more than one hundred rheumatic diseases described including inflammatory/autoimmune, osteometabolic, extra-articular/soft tissue, infectious diseases and others. Some immune-mediated inflammatory rheumatic diseases (IMRD) such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondyloarthritis (SpA) and Sjogren's syndrome (SSj) may present less aerobic capacity, more fatigue, sleep disturbance, anxiety, depression and a greater cardiovascular risk (Manzi et al., 1997; Mathieu et al., 2015; Nurmohamed et al., 2015).

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On the other hand, regular physical exercise has been described as extremely useful, inexpensive and beneficial in reducing cardiovascular morbidity and mortality in the general population, including increasing life expectancy and decreasing cardiovascular outcomes, as well as improving fatigue, aerobic capacity, quality of life and depression (Franco et al., 2005; Li et al., 2006; Thompson et al., 2003).

The European League Against Rheumatism (EULAR) recommends exercise for patients with inflammatory arthritis and osteoarthritis and suggests that aerobic conditioning, muscle strength, flexibility and neuromotor performance should be included (Rausch Osthoff et al., 2018). Regular physical exercise is also present in the treatment recommendations for SLE (Fanouriakis et al., 2019) and SSj (Valim et al., 2015).

In this chapter we will describe the main benefits of physical exercise in SLE, RA, SpA, Inflammatory Idiopatic Myopathies (IIM) and SSj.

2. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease that can affect several organs and systems (Kao et al., 2003). It has a variable incidence, with 3.8 cases/100,000 inhabitants in England (Johnson et al., 1995) and 8.7/100,000 inhabitants in Brazil (Vilar & Sato, 2002). With improved treatment and decreased mortality in recent decades, atherosclerotic vascular disease has been identified as an important cause of morbidity and mortality (Kao et al., 2003; Manzi et al., 1997). In 1976, Urowitz et al. described a bimodal pattern of mortality in the disease, prematurely due to disease activity or infection, and latterly due to complications of atherosclerotic disease (Urowitz et al., 1976). In developed countries, atherosclerotic vascular disease is responsible for up to 30% of deaths (Bernatsky et al., 2006; Petri et al., 1992). SLE women patients with age between 35 and 44 years old are 52 times more likely to present acute myocardial infarction than those without SLE of the same age (Manzi et al., 1997).

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Although previous studies have shown that SLE patients have a higher prevalence of traditional cardiovascular risk factors (Bruce et al., 2003; Manzi et al., 1997; Petri et al., 1992), the increase in cardiovascular risk is not only due to the presence of these factors (Esdaile et al., 2001), suggesting SLE related factors play an important role in the development of early atherosclerotic disease. In addition, SLE patients have greater intensity of fatigue, higher frequency of depression, worse quality of life, less tolerance to exercise and aerobic capacity and lower level of physical activity than healthy individuals (Eriksson et al., 2012).

Although the practice of physical exercise is an adjuvant treatment recommended for the treatment of the disease (Fanouriakis et al., 2019), few patients practice physical exercise regularly. In a study conducted by our group at the outpatient clinic of the Rheumatology Division at Unifesp, we found that only 15.2% of SLE patients undergo regular physical exercise (dos Reis-Neto et al., 2013). A study carried out in Sweden, found that SLE patients have less ability to walk and run and less practice of regular physical exercise. Those with damage index (SLICC) greater than two reported less physical exercise at low and moderate intensity (Eriksson et al., 2012).

Margiotta et al. (2018) evaluated 93 patients with SLE and found that 60% of them did not comply with the recommendations of the World Health Organization for physical activity, with a median of 180 (0-600) minutes a day in activities considered sedentary and 25% of the patients spent more than 6 hours in this status (Margiotta et al., 2018).

Thus, it is extremely necessary that all professionals involved in the treatment of the disease encourage SLE patients to practice physical exercise.

2.1. Physical Exercise and Aerobic Capacity, Fatigue and Quality of Life in SLE Patients

There are some studies that evaluated the effect of acute or chronic physical exercise in SLE patients (Table 1). It is worth mentioning that controversial results among the studies in the literature can be, at least

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partly, justified by differences in the modality, intensity, frequency and duration of the exercise program. In addition, supervised exercise in most of the studies may increase the chance of achieving the proposed objective.

Fatigue is one of the most frequent symptoms and interferes in the quality of life of SLE patients (Krupp et al., 1990). Improvement in fatigue is a relevant clinical outcome and often requires a multidisciplinary approach to its treatment. In 1989, Robb-Nicholson et al. demonstrated improvement in fatigue without worsening disease activity after aerobic exercise for 8 weeks in SLE patients (Robb-Nicholson et al., 1989). This finding was confirmed by Tench et al. (2003) and several other studies (Tench et al., 2003). Tench et al. (2003) in a controlled and randomized study with 93 SLE divided into 3 subgroups (home-based physical exercise for 12 weeks, relaxation and without intervention) observed improvement in fatigue in a higher percentage of patients in the home exercise group. However, they found no difference in exercise tolerance, VO_2 peak, maximum ventilation, maximum heart rate and SF-36 domains (Tench et al., 2003). Another study of the same group demonstrated less aerobic capacity, less exercise capacity, greater fatigue intensity and worse assessment in all SF-36 domains in SLE patients. In addition, they found a correlation between worse physical capacity and lower aerobic capacity, fatigue, BMI and depression (Tench et al., 2002). Keyser et al. (2003) also found lower VO_2 peak and greater fatigue in patients with SLE compared to healthy controls. In this study, 78% of patients had a fatigue severity scale above four, a score that indicates fatigue as a limitation for physical activity. They also found an inverse correlation between fatigue and VO2 peak, ventilatory threshold and test duration (Keyser et al., 2003).

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Table 1. Studies that evaluated acute or chronic physical exercise and its different outcomes in SLE patients

Author, year	n	Age (years)*	Disease activity*	Modality	VO2 max (mL/kg/ min) **	LES vs. Healthy Controls	Outcome	Disease activity effect
Robb-Nicholson, 1989	23	38.3 ± 10.9	SLEDAI: 6.6 ± 2.2	Home training (walking, running, cycling) vs. Stretching, 8 weeks	18.8 ± 4.6	NE	Improves fatigue and VO_2 during exercise	Without worsening
Tench et al., 2003	93	39.0 ± 0.8	SLAM: 5.0 (3-8)	Walking, cycling or swimming vs. Relaxation vs. Controls, 12 weeks	23.2 ± 0.7 vs. 29.2 ± 0.8 ($VO_{2\ peak}$)	Lower exercise tolerance More fatigue, depression, quality of life	Improved fatigue	Without worsening
Keyser et al., 2003	34	35.0 ± 9.0	SLAM: 3.1 ± 2.1	Cross-sectional assessment without exercise	19.2 ± 4.4 vs. 27.4 ± 4.7	Greater fatigue Inverse fatigue, VO_2max and VT correlation	--	NE
Carvalho et al., 2005	60	36.2 ± 10.8	SLEDAI: 1.1 ± 2.0	Walk, 60 minutes, 3 x HR AT vs. week. Maintain lifestyle, 12 weeks	22.6 ± 4.2	NE	Improves exercise tolerance, aerobic capacity, AT, quality of life, fatigue and depression	Without worsening
Boström et al., 2008	34	51.0 ± 10.0	SLAM: 6.5 (0-15)	Cross-sectional assessment without exercise	21.2 ± 5.2	NE	VO_2max correlation and physical capacity	NE
do Prado et al., 2011	42	29.5 ± 1.1	SLEDAI: 0.7 ± 0.3	Evaluation with ergospirometric test	27.6 ± 0.9 vs. 36.7 ± 1.1	Abnormal response to exercise HR/Chronotropic reserve		NE

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Author, year	n	Age (years)*	Disease activity*	Modality	VO2 max (mL/kg/ min) **	LES vs. Healthy Controls	Outcome	Disease activity effect
Miossi et al., 2012	36	31.4 ± 5.9	SLEDAI: 0.9 ± 1.5	Aerobic + Resistant (SLE and Controls) vs. Lifestyle (SLE), 12 weeks	24.8 ± 4.8 vs. 31.0 ± 4.8 ($VO_{2\ peak}$)	Lower peak HR, $VO_{2\ peak}$ and chronotropic reserve	Improved chronotropic incompetence and HR recovery	Without worsening
Prado et al., 2013	29	12.9 ± 2.3	SLEDAI: 5.3 ± 5.3	Aerobic, Moderate intensity, 12 weeks	27.7 ± 6.1 vs. 39.9 ± 7.3 ($VO_{2\ peak}$)	Lower peak speed, $VO_{2\ peak}$, chronotropic reserve, HR recovery	Improved time to exhaustion, HR recovery	Without worsening
Silva et al., 2013	57	29.4 ± 2.2	SLEDAI: 1.9 ± 1.5	Acute exercise	25.7 ± 5.5 vs. 32.7 ± 5.8	Lower HRmax, VEmáx and maximum speed	SLE: higher levels of IL-6 and IL-10 in the beginning. IL-6 increase in controls after acute exercise.	Without worsening
Reis-Neto et al., 2013	38	35.3 ± 6.8	SLEDAI: 2.0 ± 2.1	Walk 60 minutes 3 x week HR VT1 vs. Maintain lifestyle, 16 weeks	25.5 ± 4.4	NE	Improves exercise tolerance, maximum speed, VT1, quality of life, fatigue and endothelial function	Without worsening
Perandini et al., 2014	18	35.8 ± 6.5	SLEDAI: 1.3 ± 1.1	Aerobic, 12 weeks	24.1 ± 2.8 vs 31 ± 5.1 (VO_{2peak})	Lowest $VO_{2\ peak}$	Improvement of fatigue, Physical function (SF-36), Time in VT and at the point of respiratory compensation, time of exhaustion and peak HR, Decrease in Soluble Receptor 2 TNF and tendency to decrease IL-10	Without worsening

Table 1. (Continued)

Author, year	n	Age (years)*	Disease activity*	Modality	VO2 max (mL/kg/ min) **	LES vs. Healthy Controls	Outcome	Disease activity effect
Abrahão et al., 2016	63	43.8 ± 14.6 39.1 ± 14.4	SLEDAI: 1.8 ± 0.6 SLEDAI: 1.4 ± 0.6	Aerobic vs. Resistace vs. No exercise, 12 weeks	NE	NE	Improvement in the quality of life and physical capacity in exercise, being superior in the resisted one	Without worsening
Avaux et, 2016	45	NE	SLEDAI: 3.6 ± 3.8 SLEDAI: 2.3 ± 3.8	Supervised exercise (cycling or walking 60-80% HR maximum) and Resistance Supervised vs. Home vs. Control, 12 weeks	NE	NE	Improvement of fatigue in both exercise groups	NE
Bostrom et al., 2016	25	NE	SLEDAI: 1 (0-8)	0-3 months: Education, aerobic training 4-12 months: unsupervised activity Control group: maintaining lifestyle	21.0 ± 3.2	NE	VO_2 increase in 1 year regardless of the group	NE
Soriano-Maldonado et al., 2019	58	43.0 ± 15.1	0.04 ± 0.20	Aerobic exercise 40-75% HR Reserve, 12 weeks	NE	NE	Improves respiratory fitness. No difference in arterial stiffness, CRP, TNFa, IL-6.	NE

* Age and disease activity of SLE patients in the exercise group. ** Maximum VO_2 of patients with SLE or versus controls when assessed.

SLE: Systemic Lupus Erythematosus. VO_2 max: maximum oxygen consumption. SLEDAI: Sytemic lupus erythematosus activity index. SLAM: Systemic lupus activity measure. HR: Heart rate. AT: Anaerobic threshold. VT: ventilatory threshold. NE: Not evaluated.

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Carvalho et al. (2005) demonstrated that, after 12 weeks of supervised aerobic training at the ventilatory threshold 1, an improvement in fatigue, depression, quality of life (functional capacity, physical capacity, vitality, global health status, aspects and mental health), exercise tolerance and increased VO_2 max (Carvalho et al., 2005). Reis-Neto et al. (2013) found an improvement in exercise tolerance, maximum speed and threshold, without worsening of disease activity after 16 weeks of walking at the ventilatory threshold 1(dos Reis-Neto et al., 2013). Abrahão et al. (2016) evaluated both resistance and aerobic exercise and found improvement in quality of life and physical capacity with superior results with resistance exercise (Abrahao et al., 2016). Other groups also found similar results in improving fatigue, physical function and variables of the cardiopulmonary exercise test after aerobic training (Miossi et al., 2012; Perandini et al., 2014; Prado et al., 2013)

In a cross-sectional study, Boström et al. (2008) evaluated 34 SLE patients and found a correlation between VO_2 max and physical capacity by SF-36, but not with disease activity or damage (SLICC) (Bostrom et al., 2008). A possible mechanism involved in lower exercise tolerance and fatigue in SLE patients is the erratic control of patients' breathing during exercise, as demonstrated by Prado et al. (DM do Prado et al., 2011).

Regarding new technologies, Yuen et al. (2011) evaluated the effect of 10-week training using a Wii Fit video game on SLE patients and found improvement in fatigue, weight, waist circumference and anxiety (Yuen et al., 2011).

In a meta-analysis with 11 studies and 469 patients, O'Dwyer et al. (2017) confirmed that physical exercise in SLE patients improves fatigue, depression and cardiorespiratory capacity (O'Dwyer et al., 2017).

2.2. Physical Exercise and Cardiovascular Outcomes in SLE Patients

Physical exercise leads to a series of physiological stresses that include increased heat production, reactive oxygen species (O_2) and

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shear stress. Shear stress is the most related to the endothelium and increases during exercise as a result of increased cardiac work as a result of the increased demand for muscle O_2. To be effective in protecting the endothelium, physical exercise must be performed at an intensity capable of causing a hemodynamic response, with an increase in heart rate and blood flow. Among the cardioprotective factors influenced by exercise, the endothelium is a recognized target (Marsh & Coombes, 2005).

Paradoxically, physical exercise is recognized as an inducer of oxidative stress resulting primarily from the inefficiency of the mitochondrial respiratory chain. However, regular physical exercise increases anti-oxidant defenses and is known to be effective in preventing and treating cardiovascular disease. In vitro, the application of laminar shear stress in endothelial cell culture provides an increase in the production of free radicals and also protective factors, such as antioxidant enzymes and heat shock proteins, and decreases pro-apoptotic factors. In addition, physical exercise reduces oxidative stress by increasing the activity of nitric oxide (NO) synthase and extracellular superoxide dismutase. The effect of exercise on endothelial function results, at least in part, from increased NO bioavailability. Initially, exercise increases blood flow and the production and release of NO through mechanosensory endothelial activation, via shear stress. Subsequently, there are an increment in the production of anti-oxidants and angiogenic, resulting in reducing NO oxidation and increasing NO production, respectively. Acute physical exercise activates blood clotting while chronic practice decreases platelet activation and clotting (Marsh & Coombes, 2005). Combining all these processes, physical exercise acts as a precondition for the endothelial cell to act against mechanical or chemical injuries in cardiovascular disease.

In a cross-sectional study in SLE patients, Volkmann et al. (2010) through SF-36 and the calculation of metabolic equivalent (METS) found that a low level of physical activity - was associated with subclinical atherosclerosis and pro-inflammatory HDL (Volkmann et al., 2010).

Regarding the benefit of physical exercise on cardiovascular risk factors in SLE patients, Reis-Neto et al. (2013) evaluated the effect of

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supervised aerobic exercise, three times a week for 16 weeks and demonstrated, for the first time, an improvement in endothelial function (assessed by flow-mediated vasodilation). Endothelial dysfunction is an important marker of early atherosclerosis, a cardiovascular risk factor associated with SLE and other immune-mediated and inflammatory rheumatic diseases. In addition, there was an improvement in functional capacity and vitality; fatigue; exercise tolerance; maximum speed; ventilatory threshold speed-1 and a tendency to improve VO_2max, VO_2 at ventilatory threshold speed-1 and perceived exertion, without worsening disease activity (dos Reis-Neto et al., 2013).

Do Prado et al. (2011) demonstrated chronotropic incompetence and delayed heart rate recovery in SLE patients (DL do Prado et al., 2011) and Miossi et al. (2012) reported improvement of these factors after 12 weeks of aerobic and resistance exercise (Miossi et al., 2012).

Benatti et al. (2014) evaluated the effect of physical exercise on lipid profile and composition of HDL in 33 SLE patients (17 aerobic training for 12 weeks and 16 without training) and 11 healthy controls (aerobic training for 12 weeks). After training program, there was no difference in the lipid profile between SLE patients, however, they found a difference in the HDL_2 fraction in the trained control group (Benatti et al., 2015).

Legge et al. (2019), in a cross sectional study, evaluated 100 SLE patients without cardiovascular disease, in which only 11% adhered to moderate to intense physical activity, which was associated with improvement in blood pressure and lower cardiovascular risk score in 10 years (Legge et al., 2019).

Due to the increased cardiovascular risk and traditional cardiovascular risk factors in SLE patients, there is a concern with the assessment of patients before the beginning of physical exercise. In SLE patients without cardiovascular symptoms, Klemz et al. (2016) found 33.3% of abnormal exercise testing during assessment before physical exercise: 2.4% with arrhythmia, 11.9% hypertension during the test and 26.2% chronotropic incpompetence. SLE was the main variable associated with abnormalities in exercise testing, emphasizing the importance of carrying out a medical evaluation before the prescription of physical exercise (Klemz et al., 2016).

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2.3. Physical Exercise and Disease Activity in SLE Patients

For a long time there was a fear that regular physical exercise could worsen disease activity. However, several studies have confirmed that there was no worsening of disease activity in different modalities, including aerobic and resistance training. However, it is worth mentioning that most studies included only patients with mild to moderate disease activity, and patients with severe or even disabling disease activity were not included (Table 1).

In a meta-analysis previously mentioned, O'Dwyer et al. (2017) confirmed that physical exercise programs in SLE patients are safe, without worsening disease activity (O'Dwyer et al., 2017).

2.4. Effect of Physical Exercise on Immunological System in SLE Patients

The etiology of SLE is multifactorial. The main factors involved are: genetic, hormonal, immunological and environmental. Briefly, there is a loss of self-tolerance mechanisms with pathogenic role of autoantibodies and immune complexes and a deficiency in the clearance of apoptotic cells with consequent exposure of autoantigens on the cell surface. B cells are persistently activated by B cell activation factor (BAFF) and by T helper cells. The innate immune system is activated via the toll-like receptor 9 (TLR-9) or TLR-7 with greater production of type 1 interferons, TNFα, IL-6 and IL-10. This pattern of cytokines favors the perpetuation of the immune response. It is interesting to note that such changes may be present years before the manifestation of clinical disease (Bronson et al., 2012).

Physical exercise has an important role on immunomodulatory function, with pro-inflammatory action in acute exercise and anti-inflammatory action in chronic exercise (Gleeson et al., 2011).

Among the main effects of acute physical exercise on the immune system, we can include: transient leukocytosis (neutrophilia, lymphocytosis and monocytosis); partial suppression of cellular immunity (reduction in the number and/or function of lymphocytes and

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NK cells, possible decrease in the activity of neutrophils and monocytes and in the secretion of antibodies such as salivary IgA); increase in creatinine phosphokinase (CK), C-reactive protein (CRP), vascular adhesion molecules and cortisol; increase in muscle gene expression and cytokine concentration (TNF-α, IL-1β, IL-6, IL-10, IL-1Ra, IL-8 and IL-15); attenuated respiratory burst; reduced neutrophils chemotactic capacity of and lower expression of TLR (Gleeson et al., 2011).

On the other hand, chronic physical exercise leads to a decrease in local and systemic inflammatory condition. The main effects are: lowering production and secretion of acute phase proteins (CRP); increasing production and secretion of anti-inflammatory cytokines and improving antioxidant factors; modification of adipose tissue phenotype with anti-inflammatory pattern and inhibition of monocyte and macrophage infiltration in adipose tissue; decreased expression of TLRs in monocytes and macrophages; decrease in the number of pro-inflammatory monocytes in the blood; increased secretion of IL-6 by muscle tissue with an anti-inflammatory pattern activated by a signaling pathway involving Ca2 +/nuclear factor activated T cells (NFAT) and glycogen/p38 MAPK independent of TNF and NF-κB (Gleeson et al., 2011).

In a study with 26 SLE patients (12 sedentary and 14 physically active) and 15 healthy controls, worse endothelial function and higher levels of IL-12, TNFα and CRP were found in sedentary patients than healthy controls, with no difference between physically active patients and the controls. In addition, active patients had lower concentrations of ICAM-1 and lower SLEDAI than sedentary ones (Barnes et al., 2014).

Perandini et al. (2015) evaluated SLE patients with and without disease activity after a session of moderate and high intensity acute aerobic exercise and found that INF-y, IL-6, IL-10, TNF-α, TNFR1 and TNFR2 returned to baseline levels within 24 hours after exercise, without worsening disease activity (Perandini et al., 2015). In another study, eight SLE patients and 10 healthy controls underwent aerobic exercise for 12 weeks, twice a week, 10% below the respiratory compensation point, with a decrease in TNFR2 and a tendency to decrease IL-10 (Perandini et al., 2014).

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In order to assess the effect of acute physical exercise on serum cytokines level in SLE patients, Silva et al. (2013) submitted 27 patients and 30 controls to a treadmill acute exercise protocol and found higher levels of IL-6 and IL-10 in the baseline of SLE patients. However, after exercise, there was no change in TNF-α, IL-6 and IL-10, with an increase in IL-6 only in the control group (da Silva et al., 2013). Also evaluating the effect of acute physical exercise, Perandini et al. (2016) found a negative regulation on leukocyte gene expression in active SLE (n = 4), inactive SLE (n = 4) and healthy controls (n = 4) after a single session of aerobic exercise and a positive regulation after 3 hours of rest, although this regulation was more expressive in the control group (Perandini et al., 2016).

3. Rheumatoid Arthritis

RA is a chronic autoimmune and inflammatory disease, characterized mainly by symmetrical polyarthritis of large, medium and small joints, with the potential to affect other organs and systems. It primarily compromises the synovium, generating bone and cartilaginous destruction. The delay in diagnosis and treatment directly impacts quality of life, morbidity and mortality, with potential for progression to functional disability, loss of productivity and direct and indirect personal and social costs. It is more frequent in women in a proportion of 3:1 with age of onset mainly between 30 and 50 years. The worldwide prevalence is estimated at 0.5-1% of the population (Agca et al., 2017).

3.1. Effect of Exercise on Fatigue in RA Patients

Fatigue, as well as arthralgia and functional disability, is one of the most frequent complaints in RA patients, affecting up to 75% of patients, among which 50% considered fatigue as a score of 10 on a visual analog scale. Fatigue may be present even in inactive disease. Its etiology is multifactorial and includes: chronic pain, functional disability, sleep disorders, mood changes, medications, comorbidities,

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lifestyle and medications (Pope, 2020). In addition, fatigue and pain are cited by patients as important reasons for not starting physical exercise (Marrelli et al., 2018).

A Cochrane review identified physical activity as a potentially effective non-pharmacological strategy to reduce fatigue. Even a reduction in sedentary time is able to significantly reduce levels of fatigue (Primdahl et al., 2019).

Marrelli et al. (2018) demonstrated that resistance training is able to increase muscle mass, as well as strength and function in RA patients, reducing the risk of cachexia and sarcopenia and improving bone mineral density. In addition, it is also important in weight loss, improvement of insulin resistance and levels of CRP and IL-6. All of these factors also associated with the development of fatigue (Marrelli et al., 2018).

3.2. Effect of Exercise on Physical and Aerobic Capacity in RA Patients

Several studies have demonstrated a significant improvement in aerobic capacity through physical exercise in RA patients. Maha Azeez et al. (2020), in a study with 66 patients who underwent three months of cardiovascular and resistance exercises, found an improvement in aerobic capacity with an increase from 23.2 to 27.6 mL/kg/min (Azeez et al., 2020). Andersson et al. (2020) evaluated 24 RA patients undergoing 20 weeks of moderate to high intensity exercise, and found improvement in VO_2max (Andersson et al., 2020).

3.3. Effect of Exercise on Cardiovascular Risk in RA Patients

The increased risk of cardiovascular disease in RA can be explained by several mechanisms such as the increase in inflammatory cytokines and oxidative stress caused by the disease, changes in the composition and function of lipoproteins and endothelial dysfunction. Two meta-analyzes demonstrated a 48% increase in cardiovascular

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risk in RA patients with a 50% higher mortality rate compared to the general population (England et al., 2018). Thus, the treatment of comorbidities, especially those related to cardiovascular risk, and the disease control itself are fundamental in this process (Rausch Osthoff et al., 2018). A sedentary lifestyle is an important factor associated with cardiovascular risk in RA patients. (Fenton et al., 2017).

Stavropoulos-Kalinoglou et al. (2013) evaluated 40 RA patients who underwent aerobic and resistance training for 6 months compared to a control group receiving advice on exercise benefits and lifestyle changes and found improvement in cardiovascular risk factors (blood pressure, HDL, body mass index), disease activity (DAS28) and functional capacity (HAQ) in the exercise group (Stavropoulos-Kalinoglou et al., 2013). It has also been demonstrated by Ford et al. (2002) that RA patients submitted to an exercise program for 6 months showed a reduction in CRP levels, probably related to a reduction in body fat (Ford, 2002). Another study demonstrated improvement in micro and macrovascular function after three months of exercise in RA patients (Metsios et al., 2014).

3.4. Effect of Exercise on Disease Activity in RA Patients

There are no studies showing serious adverse effects with supervised physical exercise in RA patients.

Neuberger et al. (1997) found improvement in disease activity due to a decrease in erythrocyte sedimentation rate (ESR) (Neuberger et al., 1997). A controlled study evaluating cardiopulmonary aerobic exercise for 24 weeks in 60 RA patients with moderate disease activity demonstrated improvement in disease activity with significant decrease in DAS28 score (Peynirci Cerşit et al., 2019). A meta-analysis with 26 studies evaluating the effect of physical exercise on inflammatory diseases, amongst which 50% included studies with RA, found, with a moderate degree of evidence, the benefit of physical activity in reducing disease activity, ESR and inflammatory cytokines such as IL-17, TNF-alpha and IL-18 (Sveaas et al., 2017).

A pilot study conducted by Bartlett et al. (2018) with High Intensity Interval Training (HIIT) for 10 weeks in elderly patients with active RA

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showed an improvement in DAS28, a decrease in ESR values and an increase of 9±4% in cardiorespiratory fitness, suggesting that HIIT presents benefits in controlling disease activity (Bartlett et al., 2018). Thus, HIIT is also not contraindicated and can be encouraged in RA patients, according to their functional capacity, joint deformities and adaptations (Agca et al., 2017).

A retrospective cohort demonstrated the correlation of weight loss and the improvement of disease activity in RA patients. An improvement in the disease activity was observed in patients who presented a weight loss greater than 5 kg. The direct impact on RA disease activity probably may be related to a decrease in inflammatory markers due to fat loss (Kreps et al., 2018).

4. Spondyloarthritis

SpA comprises a group of diseases with some features that can be shared including involvement of the axial skeleton (sacroiliac and spine), peripheral joints (asymmetric oligoarthritis of large joints mainly in the lower limbs), enthesitis and extra-articular manifestations (uveitis, inflammatory bowel disease and psoriasis). The diseases that are part of this group are: ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, spondyloarthritis associated with inflammatory bowel disease and undifferentiated spondyloarthritis. Currently, there is a tendency to consider them a single disease with heterogeneous phenotypic expression (Baeten et al., 2013).

The prevalence of SpA is approximately 1%. The most prevalent disease in the group is AS with higher incidence in those with a positive family history. It mainly affects young individuals between the third and fourth decades of life, with a predominance of males in the proportion of 2 to 4:1. The predilection for males is seen mainly in AS, and in other forms of SpA the involvement of both gender is similar. It occurs more frequently in caucasians, reflecting the higher incidence of HLA-B27 antigen (Stolwijk et al., 2012).

The exercises aim to improve functional capacity, decrease pain and fatigue, improve quality of life, mobility and flexibility.

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A systematic review and meta-analysis with 14 studies and 1,579 participants with AS found that exercise can improve function, reduce pain and improve the assessment of disease activity by the patient (Regnaux et al., 2019). O'Dwyer et al. (2014), in a systematic review and meta-analysis, included 1,498 patients from 24 controlled and randomized studies, which performed breathing, resistance, aerobic and postural exercises; RPG; pilates; hydrotherapy and proprioception. This meta-analysis found that exercise improves functional capacity, disease activity and chest expansion with moderate evidence, and low evidence for improvement of pain, morning stiffness, vertebral mobility and cardiorespiratory function (O'Dwyer et al., 2014). Another systematic review performed a comparison of effectiveness between supervised and home based exercises in patients with AS and found that both can be useful in reducing disease activity and improving function, although, in the short term, supervised exercises appears to be more effective in improving disease activity (Liang et al., 2020).

Even when associated with anti-TNF therapy, physical exercises have beneficial effects on AS patients. Masiero et al. (2011) evaluated 62 patients with stable anti-TNF therapy in three groups (exercises combined with educational program, educational group alone and control group) and found improving mobility, disease activity and function in the exercise group and improved function in the educational group with maintenance of positive results for 6 months (Masiero et al., 2011).

5. Idiopathic Inflammatory Myopathies

IIM corresponds to a group of autoimmune diseases characterized by muscle weakness, mainly in the pelvic and scapular girdle, resulting from inflammatory process with consequent fatigue and decreased muscle strength (Lilleker et al., 2016; Malik et al., 2016). IIM patients are at higher risk of some comorbidities, including cardiovascular diseases and diabetes mellitus, which may also be associated with low level of physical activity and the sedentary lifestyle (Milisenda et al., 2014; Silva et al., 2016).

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Rehabilitation and physical exercise are important tools in the treatment of IIM and should be started as early as possible since they have multiple benefits, including increased muscle strength and improved quality of life and functional capacity in adults with polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM), without worsening disease activity (Alexanderson, 2012).

Most of the studies evaluating the effect of acute or chronic physical exercise in IIM patients are observational and with a small sample of patients (Table 2).

Patients with DM and PM have lower tolerance to physical exercise with anaerobic respiratory threshold 55% lower when compared to controls and lower aerobic capacity. This may be due to the component of muscle fatigue associated with inactivity (Wiesinger et al., 2000) since they have a decrease in type I muscle fibers, which are responsible for decreasing muscle resistance. On the other hand, physical exercise is able to modify the phenotype of muscle fiber with an increase in type I fibers (Dastmalchi et al., 2007). Alemo Munters et al. (2013) showed that patients with DM and PM who underwent endurance physical exercise for 12 weeks improved exercise tolerance, exhaustion time in the cycling resistance test and decreased lactate levels in exhaustion (Alemo Munters et al., 2013).

IIM patients have worse quality of life (Armadans-Tremolosa et al., 2014; Ponyi et al., 2005) with positive correlation with muscle strength and negative correlation with fatigue (Armadans-Tremolosa et al., 2014; Poulsen et al., 2017). After a 12-week resistance and aerobic exercise protocol, there was an improvement in physical function, vitality, muscle performance and VO2max in patients with PM and DM with a positive correlation of quality of life (SF-36) with VO2max. In addition, there was an improvement in disease activity, with an increase in VO2max in all those with a decrease in this parameter (Alemo Munters et al., 2013).

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Table 2. Studies that evaluated acute or chronic physical exercise and its different outcomes in IIM patients

Author, year	n	Modality	Time/Frequency/ Intensity	Disease	Outcome	Effect on Disease activity
Escalante et al., 1993	5	Resistance	8 weeks	DM/PM	Improves strength	Without worsening
Wiesinger et al., 1998	8	Aerobic	24 weeks/3x per week/60% HR max.	DM/PM	Improved functional capacity, strength and VO_2max.	Without worsening
Wiesinger et al, 1998	14	Aerobic	6 weeks/3x per week/60% HR max.	DM/PM	Improved activities of daily living, muscle strength, VO_2 max.	Without worsening
Alexanderson et al., 2000	11	Combined household	12 weeks/5x per week	PM/DM	Improvement in functional capacity and quality of life	Without worsening
Arnardottir et al., 2003	7	Exercises at home and walking	12 weeks/5X per week/mild to moderate	sIBM	No change in strength	Without worsening
Alexanderson et al. 2007	8	Resistance	7 weeks/3x per week/10 RM	DM/PM	Improved strength	Improvement
Johnson et al., 2009	7	Aerobic, resistance and stretching (home)	12 weeks/3x per week/80% HR max-15 repetitions	sIBM	Improved VO2 peak, strength, with no difference in body composition	Without worsening
Omori et al., 2012	10	Aerobic and Resistance	12 weeks/twice a week/8-12 RM and 70% VO2 MAX	DMJ	Improvement in quality of life, peak VO_2, strength and bone mineral density. Decrease in resting HR	Improvement
Mattar et al., 2014	13	Resistance training with partial blood flow restriction	12 weeks/2X per week/20-30%	DM/PM	Improvement of physical function, strength, muscle cross section, quality of life and functional capacity	Without worsening
Alexanderson et al., 2014	19	Exercises at home and walking X range of motion	24 weeks/5x per week/50-70%	DM/PM	Improvement of strength and aerobic capacity	Without worsening
Munters et al., 2013	23	Combined	12 weeks/3X per week/70% VO2 max/30-40% RM	DM/PM	Improved physical function and vitality, muscle performance, VO_2 max. Post correlation of QOL and VO_2max	Improvement

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Author, year	**n**	**Modality**	**Time/Frequency/ Intensity**	**Disease**	**Outcome**	**Effect on Disease activity**
Munters et al., 2013	23	Combined	12 weeks/3x per week/70%/40% RM	DM/PM	Improved VO_2 max. and activities of mitochondrial enzymes	Improvement
Author, year	n	Modality	Time/Frequency/ Intensity	Disease	Outcome	Disease activity effect
Munters et al., 2016	15	Combined	12 weeks/3X per week/70% VO2 MAX and 30-40%	DM/PM	Decreased inflammatory response and lactate Increased VO_2 and expression of genes related to hypertrophy	Improvement
Johnson et al., 2009	7	Aerobic, resistance and stretching (home)	12 weeks/3x per week/80% HR max/15 repetitions	IBM	Improved $VO_{2\ peak}$, strength, no difference in body composition	Without worsening
Habers et al., 2016	26	Combined home Interval training on the treadmill + strength	12 weeks	DMJ	Improved functional capacity, muscle function. There was no difference for VO_2 peak, strength, pain, quality of life and 6 min walk test.	Without worsening
Jorgensen et al., 2018	22	Resistance training with blood flow restriction	12 weeks/2x per week/Light	IBm	No difference in physical function and strength	Without worsening
De Souza et al., 2019	8	Combined	12 weeks/2x per week	IMNM	Improved aerobic capacity, strength, functional capacity and quality of life	Without worsening
Wallace et al., 2019	17	Aerobic	12 weeks/3X per week/60-80% VO2	IBM	Improved aerobic capacity	Without worsening
Oliveira et al., 2019	9	Combined	12 weeks/2X per week/8-12 maximum repetitions/ moderate	DM/PM	Improved strength, aerobic capacity, functional capacity, quality of life and decreased insulin resistance	Without worsening

IIM: Inflammatory idiopathic myopathies. DM: Dermatomyositis. PM: Polymiositis. IBM: Inclusio Body Myositis. IMNM: Immune-mediated necrotizing myopathy. VO_2 max: maximum oxygen consumption. HR: Heart rate.

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Resistance physical exercises with 8-10 maximum repetitions and moderate aerobic exercise, performed for 12 weeks twice a week, improved strength, aerobic capacity, functional capacity and quality of life in patients with DM and PM without worsening in disease activity. There was also a decrease in insulin resistance and an improvement in β-cell function (de Oliveira et al., 2019). Other studies have shown that combined physical exercise, in addition to the positive effect on aerobic capacity, is also able to improve the activity of mitochondrial enzymes, increase the expression of genes related to hypertrophy, decrease lactate and reduce disease activity (Alemo Munters et al., 2013; Munters et al., 2016).

Regarding home-based exercises, eleven patients with DM and PM at the beginning of the disease presented an improvement in functional capacity and quality of life after a home based exercise program without worsening in disease activity (Alexanderson et al., 2000). A randomized study with small sample also suggest the benefits of home exercise (Alexanderson et al., 2014). Aerobic exercise also demonstrated improvement in functional capacity, strength and VO2 max, without worsening disease activity (Wiesinger et al., 1998). Resistance exercise proved to be effective in improving strength without worsening disease activity (Alexanderson et al., 2007; Escalante et al., 1993).

Training with blood flow restriction has been recently studied in IIM patients, without any serious adverse event. A resistance training study with partial blood flow restriction in 13 patients with DM and PM demonstrated improvement in physical function, strength, muscle cross section, quality of life and functional capacity without worsening disease activity (Mattar et al., 2014).

Regarding juvenile DM (DMj), only 5% of patients perform the recommended levels of physical activity. Sedentarism has a positive correlation with disease duration and a negative correlation with VO2 levels (Pinto et al., 2016). DMj patients have a decrease of almost 30% in aerobic capacity when compared to individuals without the disease (Takken et al., 2005). Exercise program combined with resistance training (8-12 maximum repetitions) and aerobic (70% of VO_2max), f or 12 weeks, improved quality of life, strength, VO_2peak, and disease activity. Also, there was a decrease in resting heart rate (Omori et al.,

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2012). Another study with 26 DMj patients who underwent home physical exercise and interval training on the treadmill demonstrated an improvement in functional capacity and muscle function. however, without difference in aerobic capacity, strength, pain, quality of life and in the 6-minute walk test minutes (Habers et al., 2016).

Immune-mediated necrotizing myopathy (IMNM) is an entity more recently described and recognized with a smaller number of studies with physical exercise described. One study showed improvement in aerobic capacity, functional capacity, strength and quality of life, without change in CPK and disease activity after 12 weeks of combined exercise (de Souza et al., 2019).

In IBM patients, combined home exercises proved to be effective in improving aerobic capacity with no difference in body composition and disease activity. A study with aerobic training for 12 weeks, three times a week, at 60-80% of VO_2max, improved aerobic capacity of IBM patients (Wallace et al., 2019).

In this way, physical exercise is safe in IIM, without worsening disease activity. Improvements in quality of life, functional capacity and aerobic capacity are beneficial effects of physical exercise and both aerobic and resistance training, combined or with restricted blood flow, have been shown to be beneficial. IIM patients should be encouraged to practice the best physical exercise.

SJOGREN'S SYNDROME

SSj is a rheumatic disease characterized by lymphocytic infiltration and progressive destruction of the salivary and lacrimal exocrine glands, leading to dry eye and mouth complaints (Seror et al., 2010). It is classified as primary (Primary Sjögren's Syndrome – SSjp) when it occurs without any associated disease, and as secondary (Secondary Sjögren's Syndrome – SSjs) when it is associated with other autoimmune rheumatic disease, such as RA and SLE (Reksten & Jonsson, 2014; Saraux et al., 2016). It is more frequent in women between 40 and 60 years of age, with a proportion of 9 women:1 man and affects about 0.24%-0.60% of the population (Qin et al., 2015).

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Approximately 20% to 40% of SSj patients have severe systemic manifestations (Miyamoto, Lendrem, et al., 2019), mainly involving the musculoskeletal system, nervous system, lungs, kidneys, skin and blood vessels. Besides that, SSj patients may present with a decline in physical function, with decreased aerobic capacity, fatigue and a higher frequency of depression and sleep disorders with worsening quality of life and functional disability (Minali et al., 2020; Miyamoto, Valim, et al., 2019).

As in the other diseases described above, regular physical exercise has been shown as benefitial in reducing the symptoms of SSj.

Fatigue is a frequent symptom described in about 70% of SSj patients and regular physical exercise has proved to be effective as a potential treatment for this symptom (Miyamoto, Valim, et al., 2019). Pertovaara et al. (2016) found that patients who exercised more than three times a week had less fatigue and better quality of life. Wouters et al. (2011) demonstrated that patients with a high level of physical activity had less intense fatigue when compared to patients with low levels of physical activity (Wouters et al., 2012).

Minali et al. (2020), after resistance training for 12 weeks twice a week, showed an increased in strength, improved of aerobic capacity, quality of life, dynamic balance and flexibility. Strömbeck et al. (2007) demonstrated an increase in VO_2max, improvement in fatigue, depression and in the subjective scale of effort for exercise group after 12 weeks of nordic walking (Strömbeck et al., 2007). Miyamoto et al. (2019), demonstrated that, after 16 weeks of aerobic training, there was a significant improvement in VO_2max, in the distance covered, fatigue and some domains of quality of life. In addition, improvement in fatigue was associated with improved depression and quality of life (Miyamoto, Valim, et al., 2019).

Regarding disease activity, studies have shown no worsening in this parameter after intervention with physical exercise (Minali et al., 2020; Miyamoto, Valim, et al., 2019).

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CONCLUSION

Although the practice of regular physical exercise has multiple benefits for patients with IMRD and it is an useful and inexpensive strategy that can be combined with pharmacological treatment, patients still do not have adequate adherence to this practice. Rheumatologist and other professionals involved in the treatment of IMRD should encourage patients to undertake regular physical exercise.

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Chapter 7

AQUATIC EXERCISE IN THE HEALTHY POPULATION

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ABSTRACT

The practice of in-water physical activity has exponentially increased over the last decade due to the positive effects on health and physical fitness. This chapter aims to critically analyze and review the influence of aquatic exercise programs on health and physical fitness in adults. This review resulted from the analysis of different scientific articles searched in PubMed, Web of Science, and Scopus databases, including investigations that intended to analyze the changes caused by aquatic exercise programs on health and physical fitness parameters. The aquatic training programs seem to provide favorable results in most of the investigated parameters, such as muscle strength,

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cardiorespiratory fitness, certain anthropometric parameters, and lipid profile. However, these results seem to depend on several factors, such as the duration of the protocols, the intensity of the performed exercises, the nutritional control during the program, among others. Moreover, this review may also have an impact on future recommendations for planning exercise in the aquatic environment for adults and the elderly to improve the health and physical fitness parameters. Thus, we can suggest that: 1) programs lasting 12 weeks or more, combined with nutritional control, allow a decrease in fat mass and/or an increase in lean mass; 2) 8 to 12 weeks of aquatic training improves cardiorespiratory fitness; 3) 8 to 12 weeks of aquatic practice enhances/ maintains lipid profiles.

Keywords: in-water; training programs; health; fitness

INTRODUCTION

Nowadays, sedentary lifestyle is one of the main concerns of health and sports professionals (Neiva, Faíl, Izquierdo, Marques & Marinho, 2018). It is known that physical exercise is fundamental to attenuate the problems that arise from it, including reduced health status and functional capacity. However, there may be situations in which the individual's physical exercise may be restricted by low levels of physical fitness or difficulties of locomotion. These situations generally occur in obese people or in the elderly due to the physiological modifications imposed by the aging process and, consequently, they may be incapable of practicing these activities (Neiva et al., 2018; Tsourlou, Benik, Dipla, Zafeiridis & Kellis, 2006).

Thus, the aquatic environment has been increasingly recommended to facilitate physical exercise in these individuals. As a consequence, the practice of aquatic activities has increased exponentially, being an alternative method for those who are unable to regularly exercise out of the water to maintain their activity (Borreani et al., 2014; Colado, Tella, Triplett & González, 2009; Neiva et al., 2018; Tsourlou et al., 2006), as well as for people without any associated problems, including adults and healthy elderly (Colado et al., 2009).

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The aquatic context emerged as a safe environment for physical activity essentially due to the properties this environment offers, namely: 1) buoyancy - providing a reduction in the effect of body weight and compression forces on the joints; 2) drag forces - providing resistance during all movements (Borreani et al., 2014; Takeshima et al., 2002; Tsourlou et al., 2006). Therefore, due to these particularities of the aquatic environment, performing water-based activities can be indicated for any type of person, from individuals with some fragility to people without any limitation and at different ages (Borreani et al., 2014; Colado et al., 2009).

Considering the recent research on the effects of aquatic activities in adults and older adults (e.g., Bocalini, Serra, Murad & Levy, 2008; Kanitz et al., 2015; Raffaelli, Milanese, Lanza & Zamparo, 2016), it should be important to synthesize and further understand the main findings of these interventions and provide some recommendations to sports professionals. Therefore, the purpose of this narrative review was to identify and describe the effects of water-based activities in indicators of health and physical fitness, especially on cardiorespiratory fitness, lipid profile, anthropometry, and muscular strength, in adults and elder people.

METHODS

Search Strategy

For this narrative review, a search was performed in three databases (Pubmed, Web of Science, and Scopus), using the following keywords, either separately or in combination: water-based exercises, in-water, training programs, health, fitness, blood glucose, triglycerides, cholesterol, blood pressure, muscular strength, cardiorespiratory fitness, body composition, and anthropometry. Only articles written in English between 1996 and 2018 were included. Studies that focused on water-based physical activities, analyzed participants with no disease, whether adults or elderly, and assessed at least one of the following outcomes - cardiorespiratory fitness (blood pressure, heart rate, and oxygen consumption), lipid profile (glucose, triglycerides, and

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cholesterol), anthropometry, and muscular strength were included for analysis. Qualitative reviews, systematic reviews, meta-analyses, theses, dissertations, and conference abstracts were excluded.

Results

The review found that different studies used distinct methodologies, specifically programs with different durations (e.g., 8, 12, 16 or 24 weeks), use of distinct intensities of the performed exercises (e.g., 60-70%, 70-75%, 85-100%), comparing in-water with out of water interventions, with or without nutritional control to be applied during the programs and different ages of participants, which contributed to mixed results. It is also evident there has been an increase over the last years in the investigation of the effects of aquatic programs. The research is able to verify the effects of some of the aquatic exercise; however, there is a lack of studies addressing the use of these exercises by practitioners in a real-life setting.

Cardiorespiratory Fitness

Physical activity in an aquatic context can induce an increase in energy expenditure compared to the same exercise performed out of the water, as water has a much higher density than air, providing improvements in cardiovascular capacity (Meredith-Jones, Waters, Legge & Jones, 2011; Rica et al., 2013). However, to achieve these improvements in cardiorespiratory fitness, particular attention should be given to the intensity in which the exercise is performed. The exercise intensity may be monitored and programmed by several procedures, such as percentage of maximal heart rate (HR_{max}) (Bergamin, Zanuso, Alvar, Ermolao & Zaccaria, 2012) by measurement with a Polar HR monitor (Azevedo, Lambert, Zogaib & Neto, 2010; Benelli et al., 2004; Bergamin et al., 2014; Bocalini et al., 2008; Broman, Quintana, Lindberg, Jansson & Kaijser, 2006; Jones et al., 2009; Kruel et al., 2015; Lakin et al., 2013; Tsourlou et al., 2006), or percentage of maximal oxygen consumption (VO_{2max}) (Hofman & Tschakert, 2011),

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through the maximal tests using a cycle ergometer/ treadmill with a gas analyzer (Azevedo et al., 2010; Kanitz et al., 2015; Kruel et al., 2013; Lakin et al., 2013), the YMCA sub-maximal test (Neiva et al., 2018), the Balke treadmill test (Taunton et al., 1996), and the Bruce treadmill protocol (Bocalini et al., 2008). Maximum heart rate is the most commonly used method in an aquatic environment (Hofman & Tschakert, 2011), with significant improvements having been achieved in 12-week studies (Kanitz et al., 2015; Lambert et al., 2014; Raffaelli et al., 2016). Nevertheless, its use is sometimes questionable by some researchers because of the lower values of these variables in the aquatic context compared to the land environment (Benelli, Ditroilo & De Vito, 2004). This difference in values may be due to physiological changes resulting from immersion, hydrostatic pressure, or thermal conditions (Watenpaugh, Pump, Bie & Norsk, 2000). These issues regarding the water context were also found in VO_{2max} measurements. Some studies have concluded that VO_{2max} decreases when measured in water compared to similar activities performed on land (Azevedo et al., 2010; Kruel et al., 2013). In general, it is possible to understand the difficulty in the prescription of physical exercise in an aquatic context, with authors preferring to use the percentage of maximal heart rate, possibly due to its low cost and facility to apply.

To obtain significant improvements in VO_{2max}, the in-water training program should last between 8 to 12 weeks (Raffaelli et al., 2016). In agreement with this evidence are the studies by Kanitz et al. (2015) and Broman et al. (2006), demonstrating that in aquatic programs of 12 weeks, performed three times a week, and eight weeks, two times per week, considerable improvements were achieved of 41% and 11%, respectively, in VO_{2max}. However, it was shown that the order in which the exercises were performed did not produce different improvements in VO_{2max} (Pinto et al., 2014). It was suggested that the main concern should be the intensity of the exercises, particularly when working with the elderly and that the in-water exercises should be performed at moderate (70-75% HR_{max}) and/or high intensities to improve cardiorespiratory fitness (Bergamin et al., 2012). If the intensities are predominantly low, the results may not be as expected (Taunton et al., 1996).

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Muscular Strength

Several investigations have focused on the study of muscular strength and endurance in an aquatic context, with divergent conclusions. Some of the main findings in the literature showed a muscle strength enhancement after in-water exercising as a consequence of the increased stress in the muscular tissue due to the resistance imposed by the properties of the water (Bento, Pereira, Ugrinowitsch & Rodacki, 2012; Colado et al., 2009; Kanitz et al., 2015; Neiva et al., 2018; Raffaelli et al., 2016; Takeshima et al., 2002; Tsourlou et al., 2006). Some aspects are not well defined in the literature when referring to the aquatic activities and their effects on strength performance, namely the frequency of the exercises, its intensity, and the ideal order in which to exercise to obtain the maximum possible gains. Despite some uncertainty regarding the exercises order, it was suggested that during a training session in an aquatic environment, muscle strength training should be performed before aerobic training to maximize the obtained results (Pinto et al., 2014).

Although the frequency of the in-water strength training is not mentioned concerning the ideal weekly amount, it is recommended that it should be performed several times a week to increase its benefits (Borreani et al., 2014). It was also highlighted that the in-water training sessions focusing on strength maximization provided higher recovery rates than the dry land strength training, and this could increase the exercising frequency and, consequently, enhance the strength adaptations in some individuals (Borreani et al., 2014). Thus, it becomes important to understand the intensity and weekly frequency in which water activities should be performed to achieve the desired results. However, some studies do not define the used intensity, and some obtain distinct outcomes using different weekly frequencies ranging from two (Neiva et al., 2018; Seynnes, Hue, Ledrole & Bernard, 2002), three (Kanitz et al., 2015; Tsourlou et al., 2006), or five weekly classes (Carral & Pérez, 2007). Overall, we should be aware that these questions are not well established, and future studies on the intensity and frequency of strength training performed in-water are needed. (Bergamin, Ermolao, Matten, Sieverdes & Zaccaria, 2015).

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Body Composition

There are several controversies regarding the effects an aquatic training program has on anthropometric parameters and the duration required for any results. In the specific case of water aerobics, several investigations were carried out with different durations of training programs. This makes it difficult to design any possible conclusions regarding these activities and their effects.

Training programs with a maximum duration of eight or nine weeks did not produce significant changes in body composition (Jasiński et al., 2015; Raffaelli et al., 2016), and contradicting results were found with 12 weeks of water aerobics. Some results showed there were no changes in both fat and lean mass (Martinez, Lopez, Meza, Diaz & Henrique, 2014), while others evidenced improvements in body composition, mainly due to the loss of fat mass (Neiva et al., 2018). Nevertheless, higher program durations (i.e., 16 weeks) led to positive results, reducing the percentage of fat and body mass (Mendonça, Júnior, Sousa & Fernandes, 2014). Moreover, body composition was highly improved when combining aquatic exercise with nutritional control (Jasiński et al., 2015; Raffaelli et al., 2016). Thereby, when the duration of the aquatic program is equal to or greater than 12 weeks and there is extra control of caloric intake, then significant improvements in reducing fat mass and/or increasing lean mass could be generated.

Other Variables

According to the literature, it seems that aquatic exercise programs caused favorable changes in other health-related variables, such as the lipid profiles. It was verified that programs with 12 weeks of concurrent aerobic and strength training performed in water, at moderate intensities (70-75% of HR_{max}), provided reductions in blood glucose and insulin, except in overweighted women (Jones, Meredith-Jones & Legge, 2009). The same authors also reported that it was possible to obtain positive results when strength or aerobic training was performed separately (Jones et al., 2009). Regarding healthy individuals, 12

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weeks studies found significant improvements in total cholesterol, LDL cholesterol, triglycerides, and glucose (Takeshima et al., 2002). Moreover, even when the studies were not able to provide significant improvements, a maintenance of these indicators was guaranteed with eight weeks of training (Colado et al., 2009). Thus, it is noticeable that most investigations that focused on studying the effects of aquatic activities on the lipid profile, namely on glucose, triglycerides, and cholesterol, produced beneficial effects.

Another health-related parameter that benefited from the practice of in-water physical exercise was blood pressure. This variable appears to be influenced by several factors, particularly by the changes in temperature (Bergamin et al., 2015), hydrostatic pressure (Bergamin et al., 2015), water temperature (Bergamin et al., 2015), duration of the program (Colado et al., 2009), and according to the practitioners' level of physical fitness (Lakin, Notarius, Thomas & Goodman, 2013). Blood pressure seems to change as the individual moves from water to land, and vice versa, due to changes in temperature and hydrostatic pressure (Bergamin et al., 2015). Moreover, water temperature appears to be a determining factor in blood pressure changes, especially when the target population is the elderly. When a group of elderly performed physical exercise in two different situations, one in an aquatic environment with higher temperatures (36ºC) and another with lower temperatures (28ºC), there were significant reductions in diastolic and systolic blood pressure after the training program in the highest water temperature (Bergamin et al., 2015). Furthermore, it seems that the changes in blood pressure are evidenced in long-term programs. Some longitudinal studies showed relevant reductions in diastolic blood pressure, in contrast to systolic blood pressure, while other studies observed the reverse, with improvements in systolic blood pressure, but without changes in diastolic blood pressure (Colado et al., 2009; Cunha et al., 2016; Green 1989). Finally, blood pressure seems to be dependent on the level of physical fitness. A reduction of blood pressure after a training session performed out of the water was found in trained and untrained individuals, while the in-water training session showed a reduction solely in the untrained participants (Lakin, Notarius, Thomas & Goodman, 2013). This suggests the efficacy of aquatic exercise programs in untrained individuals.

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CONCLUSION

To summarize, aquatic exercise programs seem to elicit improvements in health and physical fitness in healthy individuals. The cardiorespiratory and strength performance of a healthy population seems to benefit from in-water aerobics when performed at least for 12 weeks. To improve body composition, specifically reducing body fat, more weeks (i.e., 16 weeks) are needed. The use of a higher frequency of training per week tended to maximize the benefits, as well as the use of proper intensity during exercise. It is advisable that exercises should be performed at least at moderate intensities (70-75% HRmax). These recommendations are also applied when lipid profile (cholesterol, triglycerides, and glucose) and blood pressure need improvement. Moreover, the achievements seem to be increased when the experience of the participants is inferior. There are several limitations in the current literature. Most of the training programs were not detailed and others only focused on some specific exercises, with limited variables. For instance, further investigation should be performed to improve the knowledge about the training intensity and frequency, as well as the effect of nutritional control, and regarding different age groups. Moreover, knowing that the maintenance of muscle mass and muscle strength is fundamental for the elderly, future research should also focus on this age group to try slowing down the problem generated by the aging process.

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Chapter 8

METHODOLOGICAL STRATEGIES, PLANNED MOTOR ACTIVITIES AND MOTOR ASSESSMENT IN CHILDREN AND YOUNG PEOPLE ON THE AUTISM SPECTRUM

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ABSTRACT

Over the past decade, there has been an increased prevalence of individuals diagnosed with Autism Spectrum Disorder (ASD) and consequently an increase in studies about its

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symptoms and characteristics (Myers et al., 2018). Despite the increase in individuals with this diagnosis and the number of studies that we can find in the literature, often, when parents or teachers are confronted with the diagnosis, of their children or students, it is like "plunging into the unknown." The actors in the teaching process of children on the autism spectrum (parents and teachers) often have difficulty understanding the differences in motor and social development; therefore it is necessary to examine how to assess motor, social, comunication and other abilities, among children on the autism spectrum. Moreover, it is imperative to recognize what kind of activities present major benefits and what educational strategies are more effective for this population.

With this chapter we aim to present: (i) the interrelatedness of the motor domain and other aspects of development for individuals on the autism spectrum; (ii) methodological strategies for teaching autistic children and their benefits; and (iii) testing protocols for conducting motor assessment of these individuals.

Keywords: autism spectrum disorder, assessment, motor interventions

INTRODUCTION

Autism Spectrum Disorder (hereafter referred to as autism) is a heterogeneous disorder, as it's core characteristics present differently from person to person. Furthermore, there exist several associated co-occuring conditions, both in the medical and psychiatric fields (Vargason, Frye, McGuinness, & Hahn, 2019) that do not uniformly impact each person on the autism spectrum. Though autism is considered widly to be a spectrum condition, little agreement exists about the most basic issues such as what causes or consititutes it (Waltz, 2013). In fact, autism may present more as a constellation of associated, interconnected characteristics (Hendren et al., 2009; Mumper, 2012) rather than a linear spectrum. This global lack of consensus has limited the impacts of interventions designed to improve the health outcomes of autistic individuals. Though little agreement exists and the construct of "autism" can vary from culture to culture (Hens, Robeyns & Schaubroeck, 2019), diagnosis can function as a

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starting point for theraputic assistance, as well as provide justification for an individual's difficulties (Hens & Langenberg, 2017).

According to the Diagnostic and Statistical Manual, 5th edition (DSM-V) (American Psychiatric Association [APA], 2013), autism is a neurodevelopmental disorder, whose diagnostic criteria are based on persistent deficits in communication and social interaction, as well as intense interests and repetitive behavior patterns that are classified into three levels based on support needs. In addtion to the core diagnostic characteristics of autism, autistic individuals have a higher likihood for multiple co-occuring conditions auch as attention-deficit hyperactvity disorder (ADHD), anxiety disorders, sleep-wake disorders, depressive disorder, and obsesive-compulsive disorders (OCD) (Lai et al., 2019; Rosen et al., 2018). Globally, autism has been increasingly recognized, with a current global prevalence of approximately 1 to 2% in high-income countries (Lyall et al., 2017); little data is available about the rest of the world (Elsabbagh et al., 2012).

Motor problems are currently viewed as an associating characteristic that supports the diagnosis of autism (APA, 2013). These motor difficulties have been shown to potentially act as moderators for core autistic charactersitics (Fulceri et al., 2019), can be more easily or earlier identified compared to social skills, and have been associated with the development of communication and socialization skills (MacDonald et al., 2013a; 2013b). Indeed, these differences in motor skill development are observable starting very early in a child's development. Compared to peers, delayed development of motor skills can be seen in toddlers (Lloyd et al., 2013) to young children (Ketcheson et al., 2018) to adolescents on the autism spectrum (Liu et al., 2014); though, little information is known about adult populations. Given its presentation so early in development, motor skill delays are often observable before other core characteristics—leading some researchers to suggest that motor skills be a part of the diagnositic criteria (Teitelbaum et al, 1998) or, at least, a part of screening criteria (Liu, 2012). Yet, despite the high prevalence among autistic individuals (Fournier et al., 2010), motor skill delays are not, ultimately, considered for diagnosis, nor should they be considered to be a universal occurrence.

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Motor skill development, however, is an important step toward ensuring continued engagement in physical activity (Jones et al., 2020) as well as in guiding positive tragectories for health outcomes (Robinson et al., 2015). Given the evidence of delayed motor skills among children on the autism spectrum, it is not surprising that individuals also demonstrate higher rates of physical inactivity (Healy et al, 2018; McCoy & Morgan, 2020). This lack of engagement may be attributable to a host of systemic barriers such as lack of physical access or opportunties, limited social acceptance, reduced autonomy, and minimal support networks (Blagrave & Colombo-Dougovito, 2019; Buchanan et al., 2017; Hillier et al., 2020; Nichols et al., 2019); yet, delayed motor skill devleopment during early development may have a critical role in the limited engagement in later years (Loprinzi et al., 2015). Among studies focusing on autism, there exists a great diversity of evidence reporting the existence of motor deficits, such as, basic motor, gait, balance and coordination (Kaur, Srinivasan, & Bhat, 2018), strength, agility, praxis, imitation, muscle tone, (Hilton et al., 2011) and low motor proficiency (Lourenço, Esteves, Nunes & Ting, 2020). However, the magnitude of such delays are not yet understood (Staples et al., 2012).

According to a grounded theory of the adoption and maintenance of physical activity among autistic adults (Colombo-Dougovito et al., 2020a), individual attributes such as perceived motor competence are vital in the selection of physical activities for autistic individuals. If individuals have a limited ability with the skills necessary for a physical activity, then they will be far less likely to choose or persist in that activity in the future. This is a key modifiable factor in ensuring the engagement in physical activity across the lifespan. In building competence during early years, autistic individuals may continue certain physical activities into adulthood—thus, improving many health-related outcomes as well as their quality of life (Bishop-Fitzpatrick et al., 2017). Additionally, physical activity enagagement has been shown to have moderate effects on the social functioning of young individuals on the autism spectrum, as well as a significant impact on their muscular strength and endurance (Healy et al., 2018b).

In view of all the aspects presented, with this chapter, we will present the interconnectedness of motor skills to other areas of

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development, strategies for building motor skills in youth on the autism spectrum, and suggestions for motor assessment in order to improve outcomes.

THE INTERCONNECTEDNESS OF MOTOR SKILLS

As mentioned, the motor skill development of individuals on the autism spectrum has been shown to be interrelated to, and potentially moderated by, key characteristics of autism (Fulceri et al., 2019). It has also been suggested that there is a bidirectional relationship between motor skills and social skills (Reinders et al., 2019); though, limitations with how “social skills” are defined limit our ability to more deeply explore this relationship (Colombo-Dougovito & Lee, 2020). However, evidence suggests that early motor skill development has been shown to be predictive of later expressive language and diagnosis (Lebarton & Landa, 2019). Additionally, among children and adolescents, motor skills have been shown to have a relationship with social skill development (MacDonald et al., 2013b), adaptive behavior (Bremer et al., 2018; MacDonald et al., 2013a), and with autism diagnosis (MacDonald et al., 2014). In a 2019 study, Bremer and Cairney examined further the interconnectedness of adapted behavior and motor skill. In examining the motor competence, adaptive behavior, health related fitness, physcial activity, and body composition of 27 (88.9% male) children (m = 9.9 yrs, SD = 1.7) on the autism spectrum, they found that adaptive behavior moderated the relationship between motor competence and fitness ability. Further demonstrating the intertwined nature of the traits associated with an autism diagnosis and motor skills.

This interconnected nature of motor skills to other aspects of development has led researchers to posit that by improving an individual’s motor skills, there may also be an effect on the individual’s social skills (MacDonald et al., 2013b, p. 278). Although, an increase in one construct does not necessarily result in a direct, equal immediate change in the other (e.g., Colombo-Dougovito, 2017) it is likely due to limited clarity of the social skills construct or lack of congruency during study aggregation (Colombo-Dougovito & Lee, 2020) or limitations

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within the methodology of previous empirical work (e.g., lack of longitudinal analysis). In a systematic review, Ohara et al. (2020) examined the the relationship between social skills and motor skills. In a review of 16 studies, their findings suggest that the association between motor skills and social skills was greater for fine motor skills over gross motor skills; though, they also found several studies with little association and had limited longitudinal designs within their review.

Though the evidence for how motor skills interact with other aspects of development is not clearly defined for children on the autism spectrum, it is evident that the motor domain is a vital aspect of the child's overall development. Furthermore, the importance of motor skills, and as a result motor competence, does not diminish as individuals age. As individuals age, the foundational skills developed in childhood become vital in the continued pursuit of phsycial activity (Colombo-Dougovito et al., 2020a). Importantly, physical activities and physical activity settings may provide natural settings that offer lower barriers to entry for individuals to work on social skills. These physical activity settings have a positive impact on social skills (Colombo-Dougovito & Lee, 2020), yet, too often individuals are not engaged in a meaningful or accessible way.

METHODOLOGICAL STRATEGIES FOR TEACHING

In the field of intervention, there is currently a wide variety of treatments and therapies targeted at autistic populations (Penã, 2004; Wong et al., 2015). However, many of these current intervention models have only been designed to target the core characteristics of autism. With the exception of modifying present intevention models for the physical activity setting (Colombo-Dougovito, 2015), few interventions have been designed to target the motor domain (Benevides et al., 2020). Even fewer still are interventions targeting motor skill development for autistic populations (Colombo-Dougovito & Block, 2019).

Yet, evidence suggests there are numerous benefits of physical activity for autistic individuals (Healy et al., 2018b; Sorensen & Zarrett,

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2014). Physical activity has been shown to be beneficial in improving an autistic individual's motor proficiency (Lourenço, Esteves, Corredeira & Seabra, 2015), functional, cognitive and behavioral (Sorensen, et al., 2014), social skills (Colombo-Dougovito & Lee, 2020; Reinders et al., 2019), among others. In the case of group physical activities, they can be an important contribution to the mental health of these individuals (Howells et al., 2019).

Since motor difficulties are associated with autism and several benefits associated with motor intervention programs are reported, in different domains, this type of intervention must be considered in the different interventions of a child on the autism spectrum. Yet, despite the demonstrated beneficial impacts of physical activity on the factors of quality of life for autistic individuals, this population remains less active than the general population (Gehricke, et al., 2020) and they continue to face numerous barriers to physical activity from early childhood through adolescence (Blagrave & Colombo-Dougovito, 2019; Stanish et al., 2015) into adulthood (Colombo-Dougovito et al., 2020a; Buchanan et al., 2017; Hillier et al., 2020; Nichols et al., 2019). In fact, a physical education class can be a real challenge for these children, who may have difficulties in accessing instruction, meeting with stringent rules, in learning abstract content, as well as in collective games due to the speed and exchange of functions (defense and attack) (Menear & Neumeier, 2015).

Due to motor and/or social difficulties, the actors in the teaching process of these individuals (parents and teachers) would sometimes reveal some difficulties in motor activity, as well as difficulties in understanding how to assess these individuals.

MOTOR ASSESSMENT

Assessment is defined as, "the process used to gather and analyze information to document what students have learned in a lesson, unit, or program" (Metzler, 2005). The existence of a motor skill assessment, therefore, contributes to the quantitative diagnosis and the realization of strategies in order to improve motor behavior leading to global benefits (Al Sagheer et al., 2018). It may also afford an opportunity to

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qualitatively assess an individuals ability to complete a task using a “mastery” form. Ultimately, assessments are vital to the programmatic decision needed to improve a target behavior—in this case, motor skills. Yet, there is “no one size approach to assessment” (Staples, MacDonald, & Zimmer, 2012, p. 186). With limited guidance, practitioners such as teachers, therapists, and trainers (and, even, researchers) struggle to know which tests to use to assess motor behavior.

Ultimately, a motor assessment attempts to capture an individual’s ability at that moment in time. Further, it represents the development of an individual, which allows for further observation and interpretation of the changes that are occurring throughout the development process (Rodrigues, Saraiva & Cordovil, 2014). When performed early, it can provide vital information about the motor progress of children on the autism spectrum. As mentioned, gross motor skills are delayed in children on the autism spectrum, physical activity engagement is nowhere near that of non-autistic peers, and interventions targeting motor skills are severely limited. Yet, evidence has demonstrated the importance of physical activity for autistic populations. Further, in the broader population, developing motor competence (e.g., motor proficiency, motor ability, motor performance) (Stodden et al., 2008) has been shown to have a positive impact on the overall developmental tragectories of health (Robinson et al., 2015). Motor skill proficiency in childhood has also been shown to be a predictor of physical activity engagement in adolescence (Barnett et al., 2009). Given the myriad health needs of autistic populations and limited engagement in physical activity across the lifespan, developing targeted interventions and programs aimed at improving motor competence is of the utmost importance—assessment is a key part of that process (Staples et al., 2012).

There are, however, various forms and instruments of motor assessment; yet, none of them encompass all aspects of development (Neto, 2002). This presents a large barrier for those looking to guage the motor competence of children on the autism spectrum. Though various assessment batteries have been developed to look at various aspects of motor competence, each assessment uses a different definition of motor competence—or ability, performance, skill, behavior,

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etc. Confounding issues further is the limited consensus of motor skill terminology. In attempt to clarify the difference between “motor” and “movement”—terms that are often used interchangeably—Staples and colleages (2012, p. 180) offer the following definitions:

> Movement is the observable act of moving reflecting changing in position of any body part. Motor refers to neuromuscular processes underlying a movement (e.g., balance or coordination).

In other words, movement is the process by which we observe and make inferences about an individual’s motor skill. As all assessment rely on the judgement of an assessor, this inference is heavily determined by the alignment of the motor assessment to the intended motor outcomes that are to be observed.

In considering the various motor skill assessments that exist currently, it is vital for the assessor to chose an assessment that aligns closely with the program, intervention, or evaluation goals (Liu et al., 2017; Staples et al., 2012). As children on the autism spectrum may not benefit from the typical methods of instruction as non-autistic peers, following motor assessment instructions may be difficult (Berkeley et al., 2001; MacDonald et al., 2013). Therfore, providing accommodations to standardized assessments may be necessary to accurately capture the motor competence of autistic children (Horvat, 2018). Commonly, motor assessments are provided by a verbal instruction followed by a visual demonstration (though some tests only rely on verbal instructions). Staples and Reid (2010) highlighted that, in the assessment of 9 to 12 year-olds on the autism spectrum, many had difficulty following the standardized assessment protocol. Prompting the authors to question whether autistic children truly had a “motor delay/deficit” or if they had difficulty imitating the instructor. Berkeley and colleagues (2001), in one of the earliest assessments of gross motor ability in populations on the autism spectrum, stated that many participants focused on the what of the skill (i.e., moving from point A to B) rather than the how of the skill (i.e., the locomotor form used to get from point A to B). This subtle difference in interpretation of the presented skill and potential lack of accessible communication of what was asked has large implications for the reported scope and magnitude

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of motor skill delay for children on the autism spectrum (Colombo-Dougovito, Block, Zhang, & Strehli, 2020b).

Due to the barriers in communication (APA, 2013; Wilson, McCracken, Rinehart & Jeste, 2018) that are present in the instruction of autistic children and the potential differences in the ability to imitate (Chetcuti, Hudry, Grant, & Vivanti, 2019) many have used various accommodations during the assessment procedures. It is imparitive, however, given the ubiquity of motor skill assessment in motor programing and interventions, that the assessment procedures are provided in an accessible manner (Block & Taliaferro, 2014). For many, visual cues have proved beneficial. In two related studies, Breslin and Rudisill (2011; 2013) demonstrated that providing visual cues (such as pictures or schedules) resulted in significant improvement in motor skill performances. Allen and collegues (2017), in using visual cues with the Test of Gross Motor Development, 3rd edition (Ulrich, 2019), provided further evidence of the beneficial use of visuals and suggested that visual cues had little impact on the reliability or validity of the assessment outcomes. Yet, there currently exists a lack of understanding regarding what accommodations to provide or how to provided them in an efficient manner.

In a multiple-method review, Colombo-Dougovito and colleagues (2020b) demonstrated this lack of consensus. In first conducting a literature review, the authors revealed that over 50% of the identified studies did not provide enough information to understand how the assessment was conducted—this is concerning, especially for those looking to replicate the results of those studies. Of those that provided enough information, about 19% followed the standardized procedure mentioned in the associated testing manual. About 17% used accommodations as needed; meaning that accommodations were only given when the assessors deemed it necessary. Those accommodations were: (1) additional verbal instructions, (2) additional demonstrations, (3) pictures or other visuals, (4) breaks or rewards, and (5) physical assistance. Only around 8% of examined studies used a consistent modified protocol that inluded: (1) acclimatization, (2) picture task cards, (3) picture activity schedule, and (4) additional short verbal prompts. When surveying the first authors of those identified articles, Colombo-Dougovito et al. highlighted that the researchers

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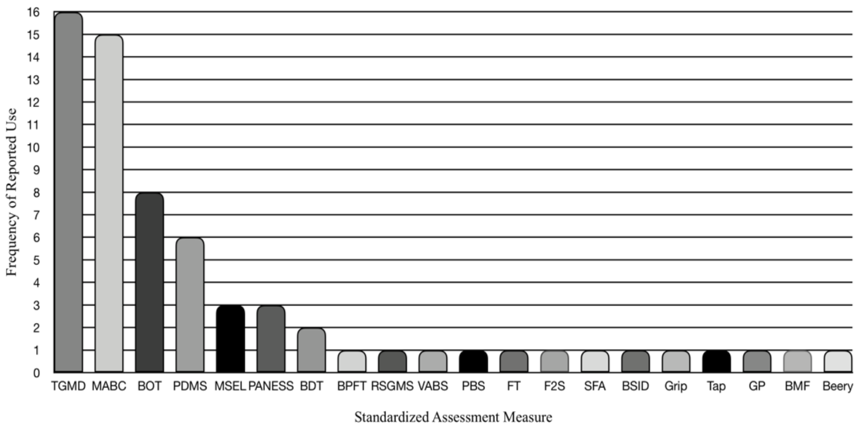
found that modifiying the protocol made the assessment seem more reliable overall and was more enjoyable for the children. These results are troubling when considing the aggregated motor assessment outcomes for children on the autism spectrum, and further stressed the question raised by Staples and colleagues (2012): Is motor impairment inate to those on the autism spectrum or is it a lack of accessible communication resulting in the evidence of delay in this population? It begs a futher question: Are the current motor assessments adequate to measure the intended motor outcomes of autistic youth?



Note. TGMD = Test of Gross Motor Development; MABC = Movement Assessment Battery for Children; BOT = Buininks-Oseretsky Test of Motor Proficiency; PDMS = Peabody Developmental Motor Scales; MSEL = Mullen Scales of Early Learning; PANESS = Physical and Neurological Examination of Subtle Signs; BDT = Battelle Development Inventory; BPFT = Brockport Physical Fitness Test; RSGMS = Rett Syndrome Gross Motor Scale; VABS = Vineland Adaptive Behavior Scales; PBS = Pediatric Balance Scale; FT = Flamingo Test; F2S = Floor to Stand; SFA = School Function Assessment; BSID = Bayley Scales of Infant Development; Grip = Grip Strength; Tap = Tapping Test; GP = Grooved Pegboard; BMF = Basic Motor Function; Beery = Beery Visual-motor Integration.

Figure 1. Breakdown of motor skill assessment used with children on the autism spectrum, as published in Colombo-Dougovito et al., 2020b.

Of the motor assessments available, the Test of Gross Motor Development (Ulrich, 2000; 2019) and the Movement Assessment

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Battery for Children (MABC) (Henderson et al., 2007) are the most prevalent (see Figure 1) (Colombo-Dougovito et al., 2020b); though, little justification is found for why certain assessments are used. As assessments should be closely aligned with the rationale for the assessment (Staple et al., 2012), practitioners should ensure that the underlying assumptions of the assessment match.

Though the TGMD is most prevalent, if the goals of the assessment are not to assess fundamental motor patterns, it will be of little use. If the goals of the assessment are to analyse the underlying motor ability (e.g., balance, coordination, or reflex), then practitioners should lean toward an assessment such as the MABC or the Bruinicks-Oseretsky Test of Motor Proficiency (BOT). If practitioners are looking to understand the developmental level a child is at, then the Physical and Developmental Motor Scales (PDMS) may be more appropriate. This must be an intentional decision by the assessor to choose the assessment that best matches the "need" for the assessment.

As prior evidence has suggested children on the autism spectrum benefit greatly from engagement in physical activity, there is a tremendous need for doctors and therapists who work with children on the autism spectrum to include motor assessments and motor interventions (Kaur, Srinivasan, & Bhat, 2018). In further determining how to select the approriate motor skill assessment, in addition to purpose, Staples and colleagues (2012) suggest that those conducting assessments also closely consider: (a) the administration of the assessment; (b) how to score and interpret the results; and (c) the ecological validity of the chosen assessment. To the first point, many assessments require training to be reliable in conducting the assessment; this may include specific ways of administering the testing items. If accommodations are to be provided, this will require further consideration for how those are provided as they will directly impact the second item to be consider, "scoring and interpretation." When considering how to interpret the results, it is important to highlight that many assessments "were developed and normed with typically developing samples, often to the exclusion of clinical [i.e., disabled] samples (Staples et al., 2012, p. 199)" though, this is slowly changing. For example, the TGMD-3 includes a more representative sample by including various children with disablies for their normative values. Yet,

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comparing the outcomes of children on the autism spectrum to normative standards should still be done with caution. To Staples and colleage third point, “Ecological Validity”, it is important to recognize that many assessments were developed and are conducted in a controlled environment; despite the fact that most motor skills are performed in uncontrolled environments and scenarios. Though motor assessment provide a glimpse of an individual’s motor competence, they do not show a complete picture nor fully represent one’s ability.

Given the demonstrated need for motor skill intervention for children on the autism spectrum, there exists many considerations regarding the types of motor skill assessment to choose, which will have a direct impact on how that assessment is interpreted. Practitioners including teachers, doctors, and therapists should closely align the chosen motor assessment with intended goals for that assessment, program, or intervention. They must, also, closely consider how to provide that assessment to the child on the autism spectrum, and how those accomodations might impact the interpration of the outcomes. Though in carefully making these decisions, practitioners will be better equiped to make the programatic decisions necessary to make impactful gains in an individuals motor skill development.

MOTOR ACTIVITIES PROGRAMS

In the last few years, several types of motor intervention programs have emerged that have been applied and studied. There are several studies presented that involve intervention programs with different activities, however all aim to understand the influence of these activities on the motor and social development of children on the autism spectrum (Lawrence & Esteves, 2019a). Figures 2, 3, and 4, below, shows some examples and planned motor interventions that have been studied recently.

In recent years, some variants in combat sports have been used by children on the autism spectrum. The techniques of Kata, Karate and Tai Chi Chuan are some examples.

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Water activities have long been described as beneficial to humans and individuals on the autism spectrum are no exception. The figure presented shows some examples of aquatic activities that have been developed.

In addition to the more specific and common areas, we can find quite diverse motor programs, as shown in the figure above, such as dance, trampolining or yoga.

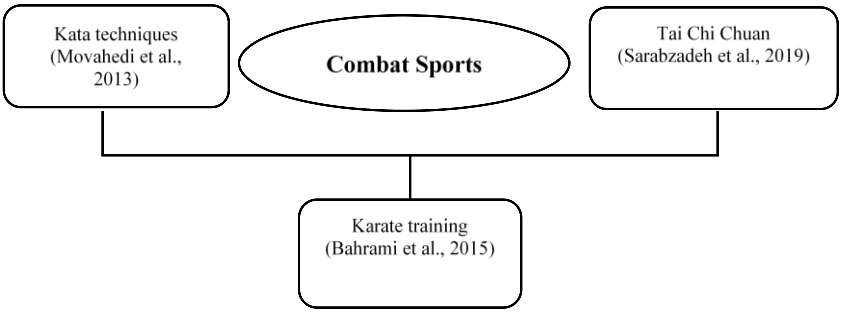

Figure 2. Intervention based in combat sports.

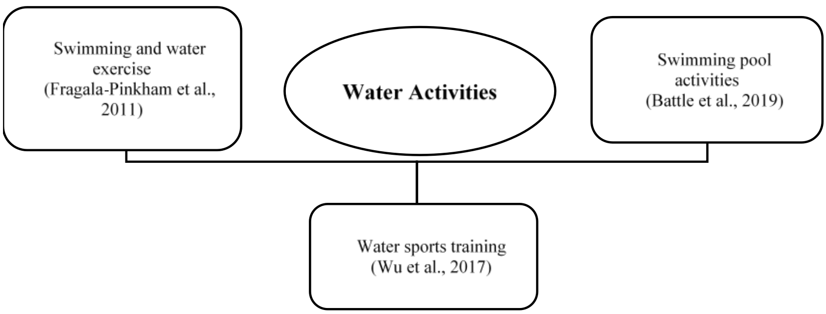

Figure 3. Intervention based in aquatic activities.

Physical activity must be guided and regular so that we can benefit from its practice. The sample (Table 1) below shows the intervention period, frequency and time of the sessions.

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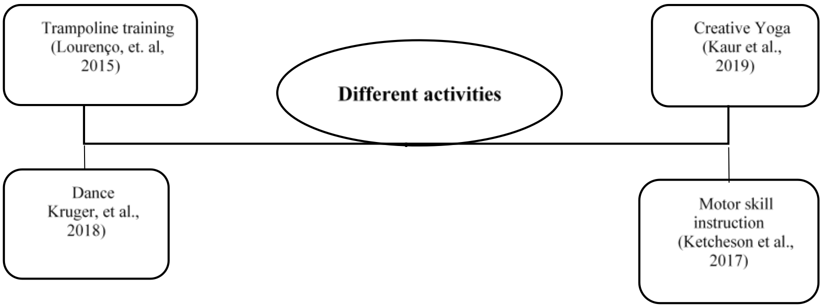

Figure 4. Intervention based in different activities.

Table 1. Physical intervention activity

Physical Intervention Activity				
	Type	**Intervention period (week)**	**Fequency (Days/week)**	**Time (Minutes)**
Combat Sports	Kata techniques (Movahedi et al., 2013)	14	4	30 m (in -8) 90 m (in 9-14)
	Karate training (Bahrami et al., 2015)	14	4	30 m (in 1-8) 90 m (in 9-14)
	Tai Chi Chuan (Sarabzadeh et al., 2019)	6	3	60 m
Water activities	Swimming and water exercise (Fragala-Pinkham et al., 2011)	14	2	40 m
	Sensory Suppote Swimming (Lawson, et al., 2016)	8	2	30 m
	Swimming pool activities (Battle et al., 2019)	12	2	45/50 m
Different activities	Trampoline training (Lourenço, et. al, 2015)	32	1	45 m
	Motor skill instruction (Ketcheson et al., 2017)	8	5	4bm.
	Dance (Kruger, et al., 2018)	14	2	50 m
	Creative Yoga (Kaur et al., 2019)	8	4 sessions (2 w expert 2 w parent)	40/ 45 m (expert) 20/25 m (parent)

Table 1 shows some motor activities programs, the duration, the weekly frequency, and the duration of the sessions of these interventions. In general, the duration of intervention programs varies between 6 and 32 weeks, although the majority takes place over a 12-

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week intervention period. The number of sessions per week varies between 1 and 5. On the session duration, most of them were between 45/50m.

CONCLUSION

The objective of this chapter was to emphasize the interconnectedness of motor skills to other areas of development and to deepen understanding of strategies of motor assessment in youth on the autism spectrum. The literature clearly demonstrates the importance of the participation of children on the autism spectrum in individualized motor intervention programs. Liu, Kaarengala and Litchke (2019) suggest that fine and gross motor skills be included in interventions or programs for autistic children. Bosa (2006) refers to the existence of four important aspects in a treatment that involves individuals on the autism spectrum: (i) social communicative stimulation; (ii) develop learning and stimulate problem-solving skills; (iii) the decrease in behaviors that impair learning and; (iv) collaboration with families to help them understand and deal with the diagnosis. In fact, we agree that, even at a young age, there should be cognitive, social and communication stimulation, which can and should be done through physical activity as it may provide more naturalistic opportunities for practice.

Therefore, with growing evidence, physical activity programs may be a vastly under utilized avenue to work on mulitiple areas of development simutaneously, such as motor and social skills. Yet, there exists little consensus about what those programs should looks like. Evidence shows that implemented physical activity programs vary greatly as to the type of activities (from combat activities, aquatic, outdoor), in the context of the activity (i.e., sports-centered or fitness-centered), as well as in the duration and frequency of these interventions (e.g., between 6 and 32 weeks and upwards of 5 times per week). Regarding strategies of motor assessment for youth on the autism spectrum, this chapter explored several problems and proposed different strategies to more successfully perform motor skills assessment. Instructors must closely consider how to provide that

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assessment to the child on the autism spectrum, and how those accomodations might impact the interpration of the outcomes.

In conclusion, further research is needed in this area, particularly focused on strategies of motor assessment in youth on the autism spectrum, in order to create and individualize physical activity programs to each child's characteristics, needs, and strengths.

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Chapter 9

EXERCISE FOR DEMENTIA: THE WAY FORWARD

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ABSTRACT

Dementia is a debilitating and progressive illness which, whilst most associated with cognitive decline, leads to extensive physical limitations and loss of independence as the person with dementia loses muscle strength, flexibility, and balance. This chapter looks at the evidence for exercise as a way of combatting some of these limitations and the practical implications of using a non-pharmacological intervention. In addition, we discuss the potential mechanisms by which exercise may contribute to the lives of people with dementia and conclude that whilst the evidence base on exercise for dementia is still emerging and evolving, there is a good pragmatic case for promoting exercise as an essential component of any intervention designed to improve the physical or psychological wellbeing of those living with dementia.

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Keywords: dementia, exercise, health, wellbeing

INTRODUCTION

Dementia is a health problem affecting some 50 million people worldwide (WHO, 2019), which is predicted to rise to over 65 million cases by 2030 (Prince, 2013). Dementia is not a single disease; rather the term is an umbrella used to describe the group of symptoms resulting from a range of progressive neurological disorders. These disorders affect the cells of the brain leading to an impairment of cognitive function beyond that expected with normal aging. The key symptoms include memory loss, confusion, mood changes, and difficulty with activities of daily living (ADL).

Although dementia is associated with older people, most commonly diagnosed over age 65 years, it can start in younger people. Depending on the type, dementia can develop slowly (e.g., Alzheimer's disease) or quite rapidly (e.g., vascular dementia), with most types being progressive. The most common type of dementia is Alzheimer's disease, but some people have more than one disease, and the distinction between them is not always clear. Dementia progresses at varying rates, affecting individuals in different ways. It is not known why one person may get one of these diseases and another might not, which means that prevention and cure are not currently possible. However, in principle, the symptoms may be ameliorated to some extent. It is felt the lives of people with dementia, and their carers/family, can be improved through early diagnosis, appropriate information/advice, supporting physical and mental health, and tackling behavioural and psychological problems (WHO, 2019).

Dementia is not solely a matter of disease affecting the person living with dementia. The impact on cognitive function is often accompanied by difficulties in everyday living, leading to a decline in physical function (Barnes et al., 2015; Blankevoort et al., 2010). Clearly that decline has a detrimental effect on ADL for the person, yet it has also been argued that the concomitant deterioration of autonomy can be a greater burden for the person's caregivers (Blankevoort et al., 2010). In addition to the cognitive impairment and decline in ADL in

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people with dementia, there can be accompanying behavioural issues. Behaviours involving agitation, irritability, wandering and nightly restlessness are not uncommon, and have been shown to have a significant impact on caregivers (Eggermont & Scherder, 2006). Also, behavioural problems can lead to a breakdown in family care and increased institutionalisation of dementia patients (Luppa et al., 2008).

It seems reasonable, then, to suggest that interventions intending to have a positive effect on physical function have the potential to be beneficial not only for the person living with dementia, but also for their careers and the wider society. It is generally recognised that exercise improves functioning (physical and mental) in older people among the general population (WHO, 2015), yet its role in those living with dementia has not received as much attention. This may reflect the fact that physical activity is relatively difficult for people with dementia due to various physical factors such as impaired balance, gait disturbances, and reduced walking speed (Atkinson et al., 2007; Eggermont and Scherder, 2006; Soumare, 2009). Pertinent here is what is meant by ‘exercise’. A useful wide definition in this context is ‘physical activity is any bodily movement produced by skeletal muscles that result in energy expenditure’ (Casperson, Powell & Christenson 1985, p. 126) to which can be added a ‘purposeful, structured and repetitive movement intended for fitness’ (Casperson, Powell & Christenson, 1985, p. 128).

Exercise as an intervention to improve the physical, cognitive, and behavioural problems experienced by people with dementia has been explored in some studies, generally looking at the potential effect on specific outcomes of exercise. However, participants in a trial tend to include different diseases and neuropathological mechanisms, and these may respond differently to different exercises, thus making it difficult to reliably identify specific effects.

In a climate of uncertainty where symptoms may be due to multiple underlying diseases with differing neuropathology, uncertainty over response to interventions, and absence of effective treatments, it is reasonable to explore the pragmatic question as whether an intervention, such as exercise, can be recommended generally for people living with dementia and, if so, what the benefits might be.

Thus, this chapter intends to provide an overarching view of what is currently known in order to help to answer some pertinent questions

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around exercise for those living with dementia. It will be helpful to know whether exercise can improve the various pertinent outcomes: physical function; cognitive function; psychological health; troublesome behaviours. We use that information to offer answers to two important pragmatic questions: is the existing evidence sufficient to recommend exercise in general and, if so, is there sufficient evidence to favour one or more types of exercise?

When thinking about exercise interventions and their potential effects, it is important to be able to quantify them in terms of frequency, intensity, type, and time (the FITT principle): the dose (FITT) of exercise is usually an important contributor to outcomes. It is known that some individuals are more sensitive to physical effort and will respond differently to the same stimulus (Herold, 2019), so the effective dose will be specific to the internal load (individual psychophysiological response) rather than external load (e.g., miles per hour). This is likely to be particularly important when looking at the effects of exercise for those living with dementia – a highly heterogeneous population.

In terms of prevention, research is still evolving, yet there is strong evidence that people can reduce their risk of dementia by making key lifestyle changes, including participating in regular activity and maintaining good heart health (Alzheimer's Association). However, that is not the topic of this chapter; rather we confine our interest to the potential for exercise to help those already living with dementia.

The following sections summarise the evidence on the impact of dementia, the role of exercise in ameliorating that impact, and the mechanisms by which exercise may have effects. That leads on to a synthesis indicating what exercise can be recommended, and presentation of evidence-informed ideas on the way forward.

IMPACT OF DEMENTIA ON INDIVIDUALS AND FAMILIES

The complex range of mental and physical health problems experienced by people with dementia change over time, and will impact on all aspects of their lives (Livingston et al., 2017). Because age is a strong risk factor for dementia, it is likely that those with dementia will also be experiencing age-related deterioration in health (Livingston et

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al., 2017). Alongside the expected cognitive decline with dementia, including reduced memory, executive functioning, and processing speed (Guardagoni, 2020; Prince et al., 2015), there is likely to be diminishing physical and social functioning. The decline in physical functioning is often referred to as a reduced ability to undertake ADL, and is associated with an inability to live independently (Rao et al., 2014), along with the burden on caregivers (Blankevort et al., 2015). Dementia, then, is a debilitating and progressive illness which, whilst most associated with cognitive decline, leads to extensive physical limitations and loss of independence as the person with dementia loses muscle strength, flexibility, and balance. Just as ageing is the major risk factor for dementia so ageing is also associated with loss of physical functioning. In addition, these people will also be at increased risk of psychological symptoms such as affective disturbances including low mood, depression, and psychotic features such as delusions, hallucinations and aggression (Fleiner et al., 2016).

Role of Exercise for Those Living with Dementia

Exercise, unlike targeted pharmaceutical interventions, has the potential to impact on the whole range of difficulties associated with dementia. Exercise in older people without dementia has been shown to improve physical and psychological wellbeing (Bangsbo et al., 2019). Exercise also has the potential to provide holistic management of the complex comorbidities of dementia (Livingston et al., 2017). Thus, the management of dementia might usefully focus on helping people 'live well with dementia', where interventions are seen as providing continuing care, rather than seeking to be curative (Livingston et al., 2017).

In order to better understand the role of exercise, we conducted a recent 'best evidence synthesis' of the evidence of exercise for people living with dementia (Lewis et al., 2020), which collated and interpreted the range and variety of studies that have been conducted to investigate the potential benefit of exercise. From a search of the main online data bases and the grey literature, we reviewed 15 high quality review articles (narrative, systematic, critical, etc.), involving a total of

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156 primary studies. The sources and key findings are presented in Table 1. In addition to these reviews, individual studies will be referenced where appropriate to further explore specific aspects of the topic.

The first question we wanted to answer is whether or not exercise can improve physical function (functional ability, fitness, walking, falls and ADLs), in people living with dementia? We deemed the evidence for a positive impact on physical function to be convincing. In particular, improving muscle strength and balance appears to improve walking ability which, in turn, leads to improved ADL (Littbrand et al., 2011). Other outcomes related to walking (walking speed, stride length, walking endurance, step length) also showed improvements (Bowes et al., 2013; Brett et al., 2016). The consistency of these findings across a number of studies and population groups suggests we can be relatively confident that physical activity improves physical function in people living with dementia (just as it does in older people without dementia).

The second question we considered is whether or not exercise can improve cognitive outcomes (cognitive function, cognitive ability) in people living with dementia? We deemed the evidence for a positive outcome on cognition to be promising. The strongest evidence of a positive relationship came from Groot et al. (2016) whose review excluded studies at risk of bias and used post-hoc meta-regression analysis to reveal no significant moderator effects for age or disease severity. Some evidence from care homes suggests exercise may prevent the decline in cognitive functioning (Brett et al., 2016), though others suggested interpreting results with caution due to the heterogeneity of the included studies (Forbes et al., 2015).

The third question was whether or not exercise improves behavioural outcomes (agitation, sleep, wandering)? The evidence for a positive outcome for behavioural outcomes we deemed as limited. Most of the studies on behavioural outcomes were set in care homes (where these outcomes are easier to measure) and some evidence of reducing wandering in people living in these settings has been reported (Barreto et al., 2015). Although there is some suggestion for reducing agitation and increasing sleep, there was insufficient evidence to be confident of an effect on this outcome.

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Table 1. Characteristics and findings of the 15 high quality reviews of exercise for people with dementia

Review authors	Type of review/ Participants	Interventions included	Outcomes measured	Outcomes with evidence of impact	FITT exercise recommended
Barreto,Demouget, Pillard, Lapeyere and Rolland (2015)	Systematic review and meta-analysis of RCTs	Strength, aerobic training, tai chi, balance and flexibility training, dance therapy and walking.	BPSD, mortality, changes in the use of antipsychotic drugs.	Depression, aberrant motor behaviour, possibly agitation, apathy and eating disorders, sleep.	FITT unknown due to the wide range of exercise interventions used.
Bowes, Dawson, Jepson and McCabe (2013)	Realist review People with dementia	Exercise of various types including dance, walking.	Cognition, mood, behaviour, physical condition.	Cognition, mood, behaviour, physical condition.	Engagement in activity may be more important than the exercise per se (for behavioural outcomes). Social and emotional dimensions of the intervention may be important.
Brett et al. (2016)	Systematic review Individuals living with a dementia in nursing homes.	Multi-modal, walking, music and movement and hand exercises.	Cognition, mood and depression, agitation, unmet needs, communication, mobility, balance, functional ability, activity level and nutrition.	Cognition, agitation, mood, mobility and functional ability.	Most common strength, balance and flexibility combined with walking. 5 sessions per week, 30 min at moderate intensity.
Cammisuli, Innocenti, Fusi, Franzoni and Pruneti (2018)	Narrative review Patients with probable AD.	Aerobic exercise	Cognition	Cognition	60% VO2 max, 30 min, 3 d/week (not clear how derived from trials).
Du, Li, Li, Zhou, Li and Yang (2018)	Meta-analysis and narrative review. Patients with c.linically diagnosed AD	Aerobic fitness, strength training, balance and flexibility training, cycling training, walking and stamina.	Cognition	Cognition	Start exercise intervention at early stage and persevere in the long run as a daily habit.

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Table 1. (Continued)

Review authors	Type of review/ Participants	Interventions included	Outcomes measured	Outcomes with evidence of impact	FITT exercise recommended
Fleiner, Leucht, Foerstl, Zijlstra and Haussermann (2016)	Narrative review People with dementia in special dementia care units.	Short term exercise intervention, including endurance and strength training exercises.	BPSD	BPSD	It may be that reducing physical inactivity is important. Challenge individual physical capacity. Positive impact of low intensity suggests it may be social stimulation not exercise itself that is important for behavioural regulation.
Forbes, Forbes, Blake, Theissen and Forbes (2015)	Cochrane systematic review People with dementia.	Aerobic, strength or balance training (or any combination).	Cognition ADLs Neuropsychiatric symptoms Depression Mortality Family care givers' burden, QoL, mortality and costs related to the use of health care services.	ADLs Family care givers' burden reduced (one trial).	Not possible to identify the FITT of exercise on the effect of ADLs or any other outcomes.
Groot et al. (2016)	Meta-analysis of RCTs Patients diagnosed with dementia.	Aerobic only, non-aerobic and combined.	Cognitive function, ADLs	Cognitive function, ADLs	The effect is driven by inclusion of aerobic activity even at low frequency (40-45min week).
Hernandez, Sandreschi, da Silva, Aracncibia, da Silva, Gutierres and Andrade (2015)	Systematic review People with AD.	Resistance, multimodal, aerobic, gym, walking.	ADLs, neuropsychiatric function, cardiovascular and cardiorespiratory fitness, functional and cognitive outcomes.	ADLs, neuropsychiatric function, cardiovascular and cardiorespiratory fitness, functional and cognitive outcomes.	Multimodal most relevant, social interaction may be important. No consensus on frequency, most studies used moderate intensity with at least 30 mins duration. Exercise should be based on goals and needs of the patient along with enhancement of life for the individual.

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Review authors	Type of review/ Participants	Interventions included	Outcomes measured	Outcomes with evidence of impact	FITT exercise recommended
Lam, Huang, Lio, Chung, Kwpk and Pang (2018)	Systematic review with meta-analysis of RCTs People with mild cognitive impairment or dementia.	Physical exercise	Strength, flexibility, gait, balance, mobility, walking endurance, dual-task ability, ADLs, QoL, falls.	Step length, balance, (high-quality); strength, mobility, walking endurance and QoL (medium quality); ADL, dual task ability and falls (low-quality); flexibility (very low quality).	More likely to achieve this with supervised multimodal exercise for ~60 mins a day, 2 to 3 days a week.
Leng, Liang, Zhou, Zhang, Hu, Li, Li and Chen (2018)	Systematic review and meta-analysis. Patients diagnosed with mild cognitive impairment or dementia.	Multicomponent, cycling, walking, strength training, dancing, tai-chi, yoga, mind-body exercise.	Depressive symptoms, neuropsychiatric symptoms, QoL, ADLs, anxiety and apathy.	Depressive symptoms, neuropsychiatric symptoms, QoL, ADLs.	Caution in the results due to the different types of exercise interventions.
Littbrand, Stenvall and Rosendal (2011)	Systematic review – qualitative analysis People with dementia.	Supervised exercise: Combined exercise (individually and group) Walking.	Physical functions Cognitive functions ADLs.	Physical functions (walking ability) ADL (some evidence).	Combined exercise, at moderate or low intensity, individual or in groups, seems applicable. Weight bearing exercise at moderate intensity for 12 months positvely affects ADLs and walking performance.
Park and Cohen (2019)	Narrative review, experimental and quasi-experimental. Older adults with various types of dementia.	Exercise (supportive exercise, aerobics, resistance exercise, stationary cycling, exercise, yoga, tai-chi, walking, dancing, multi-component exercise, mind-body exercise).	Functional ability, psychological/ behavioural or social factors.	Functional ability (beneficial), behavioural or social factors (mixed results), cognition (mild dementia).	Individualised leisure and exercise activities that are simple, with structured one-on-one social interaction.

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Table 1. (Continued)

Review authors	Type of review/ Participants	Interventions included	Outcomes measured	Outcomes with evidence of impact	FITT exercise recommended
Pitkala, Savikko, Poysti, Strandberg and Laakkonen (2013)	Review of RCTs People with dementia (separate for people in residential care and community-dwelling).	Any exercise that was planned, structured and repetitive for the purpose of conditioning any part of the body (included endurance training, strength training, balance/co-ordination, or functional exercises).	Physical functioning, mobility or related functional limitations.	Positive effects on mobility or functional limitations (6 out of 9 studies rated mod or high quality). 2 studies positive effect on physical functioning.	Frequency of intervention was at least twice per week with a progressive increase in intensity. Both group and individual effective.
Potter, Ellard, Rees and Thorogood (2011)	Systematic review Older people with dementia.	PA: Walking Lower limb strength and flexibility.	Physical function QoL Depression.	Physical function (some evidence) QoL and depression (limited evidence).	High intensity interventions which included lower limb strengthening showed the greatest improvements.

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Finally, we asked whether or not exercise leads to positive psychological outcomes (reduction in depression, improvements in mood and quality of life) for people living with dementia. We deemed evidence for a positive impact on psychological outcomes to be mixed. There was more evidence that exercise can have a psychological impact on those with severe dementia (perhaps as they are likely to be less active) than those with mild cognitive impairment (Brett et al., 2016; Leng et al., 2918). Interestingly, results also seemed dependent on the context – aspects such as who they were exercising with, and social interaction (Barreto et al., 2016; Bowes et al., 2013).

MECHANISMS BY WHICH EXERCISE MAY WORK

The influence of exercise on skeletal muscle is well established. There is an abundance of literature detailing how stress exerted on the muscle (i.e., resistance, endurance training) through exercise results in changes in muscle size (Wackerhage et al., 2019), strength (Suchomel et al., 2018) and endurance (Hawley et al., 2018) through cellular adaptation (Hughes et al., 2018). Similarly, the beneficial changes to the cardiovascular (Hellsten & Nyberg, 2011) and respiratory (McKenzie, 2012) systems are also well documented. Less, however, is understood about how exercise might impact on the brain and its function.

It has been suggested that exercise may increase the volume of the brain in older adults (Colcombe et al., 2006) and reduce atrophy of the brain in the elderly (Morris et al., 2017). In particular, exercise may increase the structure and function of the hippocampus leading to improved memory function (Voss et al., 2019). Regular exercise may also increase blood flow to the brain through increasing the number of new blood vessels (Van der Brough, 2009) and maintaining the structure and function of existing blood vessels in older people (Guadagni et al., 2020), and also throughout midlife (Barnes & Corkery, 2018). There may also be changes to levels of substances such as endocrines and hormones, which impact in particular levels of ‘brain-derived neurotrophic factors’, essential for growth factors in the central

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nervous system. This has been shown through animal studies (Voss et al., 2019) but is also likely to be a factor in humans.

Finally, there are social, emotional and psychological mechanisms that may play a part. Physical activity is emerging as one of the most powerful tools for many geriatric syndromes (Vengas-Sanabria et al., 2020) as the physical effects of ageing can be attenuated and, in some cases, reversed through increased physical activity (Bangsboo et al., 2019). At the same time physical activity and its role in mental health is also gaining ground as the importance of the well-established links between mind and body (Sarobji, 1974) are being scientifically studied and verified (Levine et al., 2021). Dementia is diagnosed as a cognitive impairment but it's impact on individuals is both mental and physical. Physical activity impacts on both the mind and the body of the individual, yet exercise studies in dementia have, in the main, looked for a role of exercise in preventing and treating cognitive decline. However, there are now an increasing number of studies looking at the potential for exercise in managing the physical, behavioural, and psychological difficulties associated with dementia. It may be that the benefits of being active for those with dementia may not solely be on improving cognitive function but on improving physical function (which then impacts on behavioural and psychological issues).

Previous study has generally focused on specific impact outcomes associated with dementia, but few studies have looked at the cumulative impacts on the individual as a whole, and even fewer have looked at the impact of dementia from the perspective of the person and how they experience life with dementia. When looking at the research literature on physical activity and ageing we can see that maintaining activity into old age can prevent the physical decline associated with older age and that it is inactivity, not age per-se, that leads to many problems associated with ageing. We also know that for those with dementia, in particular in care home settings, being inactive is the default. It has been reported that people in care homes spend up to 94% of their waking time sat down (Whear et al., 2014). When dementia is treated solely pharmacologically, people with dementia passively receive treatment with little investment in them as individuals. When dementia is treated with non-pharmacological methods, such as exercise, individuals are actively involved in their management and will

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experience being 'invested in' by those providing the intervention (Olsen et al., 2015).

Qualitative research has suggested that people with dementia, even those with advanced dementia, can and should be involved in decisions surrounding their care (Bokberg et al., 2014; Whitlatch et al., 2009). Qualitative research can provide useful insights both from the individual with dementia, their family and carers (van Baalen et al., 2011). Olsen et al. (2015), undertook a study of high intensity functional activity in a care home setting with people with dementia, using interviews as well as functional measurements to investigate the impact. Not only did the study show that exercise led to improved physical function but the participants enjoyed the exercise and reported improved emotional wellbeing. The authors discuss their findings within the self-efficacy framework. Self-efficacy is defined as 'a person's belief in one's own capacity to accomplish specific tasks and behaviours' (Banduara, 1997) and has often been used as an explanation for the impact of physical activity on mental health. Tonga et al. (2020) found the significant relationship between self-efficacy and quality of life was due to a reduction in depression and anxiety in the individuals with dementia. In the Olsen et al. (2015) study, the exercise intervention allowed individuals to feel in control of their treatment because they were actively involved and, although they felt challenged, their ability to accomplish the exercise led to feelings of mastery. This, combined with the involvement of physiotherapy staff and the group nature of the exercise class, led to vicarious experiences. This suggests that the power of physical activity is not just in the exercise and the volume of activity, but also the social environment in which it is delivered, along with the confidence in the delivery from the instructor, that is essential in delivering benefits (Hawley-Hague et al., 2017). Whilst we can quantitatively measure the impact of exercise interventions on the elderly, it is only through qualitative research and listening to their experiences that we can begin to understand the holistic impact on the individual. The Olsen et al. (2015) study was only one small scale study but it does show the value of including qualitative research when exploring the impact of physical activity for those with dementia.

Bowes et al. (2013) in their scoping review of the literature on physical activity with dementia, included interviews with service

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providers in order to understand the impact of physical activity from the perspective of those delivering it. The interviewees described witnessing physical benefits and also emotional and social benefits among participants. Pleasure and enjoyment were seen to be derived from participating in the physical activity and individuals socialised more after the classes. Again, they describe participants being able to do something for themselves and improving their skills, thus leading to positive emotions. In particular, in care homes, it was seen as important for relieving daily monotony and providing something for the residents to do. Bowes et al. (2013) was another small-scale study and may not be viewed as 'scientific evidence'. However, when considering complex health conditions and the impact of complex interventions (such as exercise), the gold standard of randomised control trials (RCT) only tells part of the story, and can fail to provide 'real world' answers. Whilst systematic reviews of RCTs are traditionally considered the best form of evidence, this hierarchy of evidence has recently been questioned (Greenhalgh et al., 2018; Lewis & Burton, 2020). Narrative reviews that are well conducted, can include a wider range of evidence and help make sense of complex issues and draw conclusions on the balance of that evidence. If we cannot break down physical activity into its component parts (physical, emotional, psychological) then we need to study its holistic impact on individuals through understanding the experiential impact. This cannot be objectively quantified and needs the exploration of thoughts and perceptions of individuals to understand what it means to them as human beings not just human bodies.

WHAT EXERCISE SHOULD WE BE RECOMMENDING?

It is clear that dementia impacts on individuals' lives in many ways beyond cognitive decline. To reduce the impact of a variety of degenerative outcomes requires a variety of exercise modalities. In addition, inter-individuality of people living with dementia makes it impossible to provide a 'one size fits all' prescription (Muller et al., 2019). This probably explains why the majority of exercise programmes used in research studies are 'multi-modal' (two or more types of

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exercise). However, there is evidence that certain types of exercise lead to specific types of outcomes. To improve strength (and therefore ability to perform ADL) resistance based exercises, two to three times are week, are recommended (Lam et al., 2018). Cognitive outcomes appear to respond best to multiple tasks and aerobic exercise (Brett et al., 2016; Hernandez 2015). Psychological outcomes require exercise to be enjoyable and supported (Barreto et al., 2015; Bowes, 2013; Olsen et. al, 2015). For some individuals this may mean exercising outdoors (Pollock, 2012), with music (Rehfield et al., 2018), or include social interaction (Barreto et al., 2015; Bowes et al., 2013; Lamotte et al., 2017). We also have to consider not only what exercise an individual may enjoy but also what they are capable of (which will depend on their baseline fitness as well as severity of dementia).

THE WAY FORWARD

Whilst the evidence base on exercise for dementia is still emerging and evolving, there is a good pragmatic case for promoting exercise as an essential component of any intervention designed to improve the physical or psychological wellbeing of those living with dementia. We do not need to wait for more robust evidence to understand that exercise should be part of all lifestyles, regardless of cognitive decline. If designed to suit the individual's needs it may prove to be an essential aid to living well with dementia.

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Chapter 10

BENEFITS OF AN ACTIVE LIFESTYLE FOR WOMEN LIVING WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder affecting a large proportion of women worldwide. It is characterised by hyperandrogenism, insulin resistance, hirsutism, acne, menstruation abnormalities, and infertility. For women living with PCOS there is an increased risk of overweight or obesity, dyslipidaemia, hypertension, metabolic

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syndrome, and type 2 diabetes. The biopsychosocial nature of the condition can also have a significant negative impact on women's health-related quality of life and psychological wellbeing. However, there is emerging evidence to suggest that regular physical activity and exercise can improve health and alleviate symptoms. Therefore, this chapter aims to inform the reader about the psychological, physical, and physiological benefits of exercise and physical activity for women living with PCOS.

Keywords: polycystic ovary syndrome, wellbeing, active lifestyle

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common endocrine and metabolic disorder affecting 8–20% of reproductive aged women, depending on the diagnostic criteria used (e.g., March et al., 2010; Yildiz et al., 2011; Bozdag et al., 2016). The Rotterdam criteria are internationally accepted and require any two of the following three criteria: oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasonography (Teede et al., 2018). Consequently, PCOS is characterised by hirsutism, clinically significant acne, elevated serum androgens (e.g., testosterone), menstruation abnormalities, and infertility. Some research has demonstrated an association between the prevalence of PCOS and ethnicity (Davis et al., 2002), although other research suggests similar prevalence rates between Caucasian people of European decent, African-American, and Mexican women (Wolf et al., 2018). For women living with PCOS, it is a very stigmatising condition and can have detrimental effects on mental health and psychological function (Deeks et al., 2011; Blay et al., 2016; Wright et al., 2020). The effects of living with PCOS on long-term physical health are also well known within scientific literature. These include increased risk for overweight and obesity, dyslipidaemia, insulin resistance, metabolic syndrome, type 2 diabetes, and cardiovascular disease (CVD) (Cussons et al., 2008; Stepto et al., 2013). Furthermore, hyperandrogenism might exacerbate these risk factors.

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For these reasons, leading an active lifestyle is considered a cornerstone for the management of PCOS. The terms “physical activity” (PA) and “exercise” are frequently used interchangeably although imprecisely. A universal definition of exercise was proposed by Winter & Fowler (2009) as: ‘a potential disruption to homeostasis by muscle activity that is either exclusively or in combination concentric, isometric or eccentric’. Using this suggestion, the practical difference between exercise and PA is minimal. However, for many people, including women with PCOS, “exercise” is frequently viewed as competitive sport or gym-based activity and perceived to be unpleasant or intimidating (Biddle & Mutrie, 2008), whereas the terms “physical activity” and “active lifestyle” are considered more user-friendly and describe unstructured activities of daily living such as stair climbing and walking during occupational and leisure-related tasks. In this chapter the two terms will not be used synonymously. “Exercise” is considered a distinct subset of physical activity, characterised by planned, structured, and repetitive leisure-time pursuits purposefully focused on improvement or maintenance of any component(s) of physical fitness; whereas “physical activity” refers to any bodily movement produced by skeletal muscles that increases energy expenditure (Caspersen, Powell, & Christenson, 1985).

Current best-evidence PA guidelines from the World Health Organisation (WHO) recommend adults undertake 150–300 minutes of moderate-intensity, or 75–150 minutes of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity, per week (Bull et al., 2020). Regular muscle strengthening activities are also recommended on two non-consecutive days per week. Meeting these recommendations is associated with a lower lifetime risk of CVD in men and women (Kubota et al., 2018; Lachman et al., 2018). “Physical inactivity” refers to the non-achievement of PA guidelines (Thivel et al., 2018). For example, in the UK, anybody not meeting the 150 minutes per week of moderate, or 75 minutes per week of vigorous intensity aerobic exercise would be classed as physically inactive. “Sedentary behaviour” is defined as any waking behaviour characterised by an energy expenditure ≤ 1.5. metabolic equivalents (METS) while in a sitting, reclining, or lying posture (Tremblay et al., 2018).

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Guidelines for PCOS are broadly similar as outlined in the International Evidence-based Guideline for the Assessment and Management of PCOS (Teede et al., 2018). One distinction is that the PCOS guidelines suggest PA be performed in at least 10-minute bouts, aiming to achieve 30 minutes daily on most days, whereas the more recent WHO recommendations have removed this stipulation. This is based on evidence from cross sectional and cohort studies, which show PA of any bout duration is associated with improved health outcomes, including all-cause mortality (Ekelund et al., 2019; Jakicic et al., 2019). It is reasonable to speculate that similar favourable health outcomes would be experienced by women living with PCOS. Importantly, both structured exercise interventions and PA have demonstrable health benefits in PCOS. For example, Mario et al. (2017) reported that habitual PA (defined as 7500 daily steps) over a period of five-years was associated with a healthier anthropometric and androgenic profile in women with PCOS compared to inactive women with PCOS. Furthermore, an increment of 2000 steps per day was independently associated with a decreased free androgen index (i.e., regardless of PA status).

Lifestyle advice typically focuses on dietary and PA recommendations with the aim of weight loss, including caloric restriction, without specific recommendations for diet composition or modes of PA. However, it is important to highlight that the perceived benefit of exercise and PA in healthcare and public discourse frequently seems to reside in the association with weight loss. This is especially true for women with PCOS struggling to lose weight, or for those that are overweight and struggling to conceive (and would like to be considered for fertility treatment) due to the general association between obesity and infertility (Dağ & Dilbaz, 2015). Whilst this is unequivocally important, it is also important to realise that an active lifestyle provides benefits irrespective of weight or fat loss. Exercise-induced reductions in cardiometabolic risk factors including insulin resistance, triglycerides, and visceral adiposity have been observed without significant weight loss reduction in women living with PCOS (Hutchinson et al., 2011). As such, lifestyle intervention is applicable to all women with PCOS and should be considered a principal focus of treatment regardless of weight or fertility status (Krystock, 2014; Legro,

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2017; Teede et al., 2018). Focusing on weight loss as an outcome alone, or only recommending lifestyle changes to women with overweight or obesity and PCOS, fails to acknowledge the wide-ranging impacts of PA.

Physical Activity and Exercise Interventions in Women with PCOS

PA and exercise interventions for as little as 10-weeks have been shown to improve a variety of health-related outcomes, including both cardiometabolic risk factors and reproductive capacity markers (Harrison et al., 2011; Patton et al., 2020). Indeed, there have been a wide range of lifestyle interventions, including both dietary and pharmacological components in conjunction with PA. However, there are fewer interventions that assess PA in isolation, making it difficult to elucidate the most important parameters for an effective intervention. Furthermore, variation in population, study design, and intervention design have led to varying and sometimes conflicting results.

In 2011, Harrison et al. conducted the first systematic review to identify the independent effects of exercise on cardiovascular and reproductive outcomes in women with PCOS. They found a lack of randomised controlled trial (RCT) designs, and thus captured cohort studies as well. Even then, only eight studies were identified where exercise could be assessed independently. Sample sizes varied considerably, with enrolled participants ranging from 12 to 124. All studies included participants with overweight or obesity, with a mean body mass index (BMI) range of 26.8 to 37.9 kg/m2, and all participants were pre-menopausal. Six of the eight studies were aerobic exercise only, while the other two incorporated resistance training either alone or in combination with aerobic training. Furthermore, duration and frequency varied considerably, from 12 weeks up 20 weeks, with participants exercising between three to seven sessions per week. Although not a meta-analysis, the synthesis indicated that sustainable, less intensive studies, or those of a shorter duration, were likely to result in significant clinical benefits. These included improvements in ovulation and menstrual cycle regulation, weight loss (4.5–10% of body

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mass), and a 9–30% reduction in insulin resistance, in young women with PCOS.

Since then, various other reviews and meta-analyses have been conducted to further elucidate the efficacy of PA and exercise on menstrual, cardiometabolic, and mental health outcomes in PCOS (Benham et al., 2018; Domecq et al., 2013; Haqq et al., 2015; Kite et al., 2019). However, several of these reviews reported results where exercise, dietary intervention, and pharmacological intervention were combined (or did not indicate if exercise was in isolation) or did not exclude participants already taking metabolism altering medications such as metformin or the oral contraceptive pill. Thus, despite the high quantity of reviews in this area, there remains a lack of high-quality evidence to determine the specific parameters (e.g., mode, frequency, duration) of effective PA interventions, in isolation, for women living with PCOS.

Treatment for PCOS typically focuses on alleviating and managing symptoms rather than attempting to treat the origin of the condition, which is not necessarily known and may not be amenable to treatment. Thus, the individual presentation of PCOS symptoms plays a role in the choice of treatment for each individual. To address specific symptoms, treatment typically includes lifestyle advice including the programming of PA and exercise and reduction in sedentary behaviour, which is the focus of this chapter.

A Note on Translating Exercise and Physical Activity into ‘Real World’ Strategies

Encouraging any person to lead a healthier active lifestyle is inherently challenging because interactions between behavioural, biological, and environmental factors are complex. Superimposed over this challenge, the management of PCOS is additionally difficult because the pathogenesis of the condition is also complex and not completely understood. Therefore, attempts to tackle problems such as exercise and PA for women with PCOS use complex interventions, conventionally defined as having several interacting components. Such approaches can be practically and methodologically difficult, thus, as

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already mentioned, limited research assesses PA in isolation, making it difficult to elucidate parameters for an effective intervention because causal effects linking intervention with outcomes can be complicated. Consequently, it is important that sufficient initial development of interventions is undertaken to consider methodological bias and imprecision that could undermine eventual implementation in practice (for example, see Woodward et al., 2020).

Many health care interventions fail to demonstrate effectiveness when translated to demonstrable benefits in real-world contexts (Øvretveit, 2004; Collier, 2009). This is relevant for exercise and PA interventions because, although evidence for their efficacy in treating disease is strong, frequently there is a dearth of evidence for their effectiveness in real-world settings (Beedie et al., 2015). Many studies intending to examine effectiveness use laboratory-style methods and controls that would be impractical and uneconomical in real-world interventions (Beedie et al., 2014), and these concerns are potentially decisive because effectiveness is what matters to patients and commissioners (Beedie et al., 2015).

Women with PCOS are likely to present with a multitude of interacting problems challenging engagement with and the sustainability of exercise and PA interventions as a management strategy. Despite the potential for benefits, women with PCOS are likely to receive limited specific lifestyle advice and the efficacy of different types and intensity of exercise on PCOS and its associated co-morbidities remains unclear. Furthermore, women with PCOS are likely to have several barriers to exercise and PA including fear of injury, physical limitations, and low confidence to maintain activity (Banting et al., 2014). This requires women to be supported with empathy and understanding using broad perspectives of health and wellbeing. The emotional impact of living with PCOS should also not be underestimated since the disorder has the potential to deeply undermine women's self-esteem and affect their perception of feminine identity. As such, health professionals should be aware of impacts on emotional wellbeing and on quality of life (Teede et al., 2018), and prescribing exercise or PA for women with PCOS should be individualised and consider both common and PCOS-specific barriers and motivators for successful engagement. Accordingly, to further the

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research agenda, an aim of future studies should be to address the effectiveness of exercise and PA strategies in "real-world" settings to determine if benefits are retained outside of controlled environments.

Psychological Benefits of Exercise

The Role of Exercise and Physical Activity in Depression in Women with PCOS

PCOS is associated with diminished mental health. A meta-analysis of 10 studies reported increased depressive symptoms in 44% of women with PCOS compared to 17% of women in control groups (odds ratio [OR] = 4.03) (Dokras et al., 2011). Other meta-analyses have also reported higher rates of depressive symptoms in women with PCOS compared to women without PCOS (OR = 3.51), and that the magnitude of these differences are large (Hedges' g effect size = 0.82) and likely to be clinically significant (Barry et al., 2011; Blay et al., 2016). Cross-sectional research has identified perception of body image, self-worth, and quality of life (QoL) as predictors of depression (Deeks et al., 2011). Exercise and PA are purported to ameliorate depressive symptoms and a Cochrane review of 39 trials demonstrated exercise is moderately more effective than a control intervention for reducing symptoms of depression in women without PCOS (Cooney et al., 2013). There are several plausible mechanisms why an active lifestyle might improve depression including changes in self-efficacy which might be linked with self-esteem and subjective well-being (Craft, 2005; Annesi, 2012), social support (Miller et al., 2019), and to a lesser extent distraction from negative thoughts (Craft, 2005). Exercise and PA could also have physiological effects such as changes in the concentrations of endocannabinoids (Dietrich & McDaniel, 2004), monoamines (i.e., dopamine, noradrenaline, and serotonin) (Lin & Kuo, 2013), and cortisol (Beserra et al., 2018), in addition to exercise-induced neurogenesis (i.e., synthesis of new neurons in the brain) (Ernst et al., 2006), all of which can improve mood. These antidepressant effects might also manifest in women with PCOS.

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In a review of seven papers that considered mental health outcomes, Conte et al. (2014) reported that PA is likely to be beneficial to the mental health of women with PCOS. However, the current literature is insufficient to identify isolated effects of exercise or PA on PCOS, given the complex management of the disorder which also includes changes to diet and pharmacotherapy. Other research has demonstrated that active women with PCOS report fewer depressive symptoms compared to women with PCOS who are inactive, although active women with PCOS still have higher depressive symptoms than active women without PCOS (Banting et al., 2014). In a cross-sectional study of 146 women with PCOS (70% with overweight, 48% with obesity) who visited a multidisciplinary PCOS clinic, being active was associated with lower mean scores on the Beck Depression Index (OR = 2.67 for inactive women with PCOS) and lower prevalence of mild depression. Furthermore, the association between PCOS and depression also remained significant after adjustment for age, ethnicity, and BMI. This large observational study is important because it is more likely to highlight associations that reflect sustainable exercise and PA behaviours in the "real-world", rather than the controlled circumstances of an intervention trial which does not necessarily establish effectiveness in free-living conditions. The meta-analysis by Barry et al. (2011) suggested that women with PCOS with lower BMI tend to have slightly lower depression scores, suggesting that having a lower BMI reduces depression, which agrees with previous research suggesting an association between obesity and depression in PCOS (Rasgon et al., 2003).

There is a strong rationale for exercise and PA improving depressive symptoms in women living with PCOS. However, management of the disorder is complex, and it is currently not possible to identify the independent effects on PCOS. Several characteristics of PCOS, such as hirsutism and infertility, are likely to be independently associated with poorer mental health and might remain unresolved despite a more active lifestyle, so could conceivably diminish the effects of exercise and PA on mental health in women with PCOS. Nevertheless, research suggests that PA is a positive intervention for directly improving psychological functioning, not just via association with physiological improvements (e.g., weight loss or improved fertility)

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(Conte et al., 2015). It is also an intervention that appears to have no adverse effects.

The Role of Exercise and Physical Activity in Anxiety in Women with PCOS

Whereas depression is generally seen as a single illness with lots of different symptoms, anxiety is an umbrella term that encompasses a range of conditions including generalised anxiety disorder, phobias, panic disorders, adjustment disorder, and stress reaction. In a population-based retrospective cohort study in Australia (2566 participants) the incidence of documented clinical anxiety disorders in women with PCOS was significantly higher compared with women without PCOS (14% and 5.9%, respectively) (Hart & Doherty, 2015). Several meta-analyses also show that women with PCOS have significantly increased risk of moderate and severe anxiety symptoms (Barry et al., 2011; Veltman-Verhulst, et al., 2012; Cooney et al., 2017). For example, Cooney et al. (2017) found increased odds of any anxiety symptoms (OR = 5.62) and of moderate or severe anxiety symptoms (OR = 6.55), and found the risk to be independent of obesity, but weakly associated with age, BMI, elevated testosterone, hirsutism, and insulin resistance.

Some evidence supports that exercise and PA can reduce anxiety in women with PCOS. In a clinical trial, 57 women with PCOS carried out either continuous or intermittent aerobic exercise for 16 weeks and reported lower anxiety after the intervention compared to control (Kogure et al., 2020). However, in a cross-sectional, observational study, engaging in PA (self-reported and defined as agreement with the active or maintenance stages of the trans-theoretical model) was not significantly associated with lower anxiety after controlling for age, BMI, and PCOS status (Banting et al., 2014). The reason for the discrepancy in these results is not clear but could be explained by the self-reported PA, differing geographical locations (Brazil and Australia, respectively), or participant heterogeneity in terms of BMI and age. A higher BMI was associated with greater anxiety (Banting et al., 2014) which is consistent with other research (Zhao et al., 2009). As such, an active

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lifestyle could indirectly influence anxiety through mediating effects on body mass.

The Role of Exercise and Physical Activity in Quality of Life in Women with PCOS

Health related quality of life (HRQoL) is a well-recognised and important health outcome for several chronic conditions and relates to the physical, social, and emotional effects of a condition and its associated treatments (Moran et al., 2010). Assessment is self-report, typically via the Short Form-36 (SF-36) questionnaire. Alternatively, for women with PCOS, the PCOS-Questionnaire (PCOS-Q) includes additional domains in relation to emotions, body hair, weight, infertility, and menstrual abnormalities; and the Modified PCOS-Q (MPCOS-Q) also includes an acne domain (Jones et al., 2004; Malik-Aslam et al., 2010). In a meta-analysis, studies consistently reported reduced HRQoL scores in women with PCOS, compared with control groups and normative population data. Infertility and weight concerns had the most significant impact (Dokras et al., 2018). In a separate meta-analysis, Bazarganipour et al. (2015) showed that hirsutism and menstruation are also key domains associated with lower HRQoL scores.

Lifestyle changes, incorporating diet, exercise, and behavioural interventions, in women with PCOS were considered in a recent Cochrane review (Lim et al., 2019). Comparing lifestyle treatment to minimal treatment, evidence for a small beneficial effect on PCOS-Q scores in the domains of emotions and infertility were reported, although heterogeneity was high. However, the effects of lifestyle treatment on the domains of weight, hirsutism, and menstrual regularity were less certain. Similarly, in a systematic review and meta-analysis that included three eligible trials, there was no evidence of effect in any of the PCOS-Q domains in an exercise versus control comparison, although scores were improved in the physical functioning, general health, social functioning, and mental health domains of the SF-36 (Kite et al., 2019). Improvements in these outcomes were ≥ 10% for exercise compared with control, providing some evidence to suggest that

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exercise might improve women's perceptions of physical and mental wellbeing. Again, the effects of a supervised aerobic exercise training intervention (~150 minutes per week over 16 weeks) on HRQoL was investigated in a randomised controlled trial in overweight and obese women with PCOS, with significant improvements in physical functioning, general health, and mental health domains reported (Costa et al., 2018).

It is less clear if the findings of controlled trials can be retained outside a controlled setting. Furthermore, the current evidence is of low quality with inconsistent and imprecise findings, and poor reporting of the methods used in the studies (Lim et al., 2019). This is compounded by using generic quality of life tools that are not tailored to women living with PCOS, yet they are the only tools that can compare HRQoL between women with and without PCOS (Dokras et al., 2018). Heterogeneousness in results concerning the effects of an active lifestyle on quality of life in women with PCOS is to be expected considering the complexity of the disorder and that HRQoL is not only affected by anxiety, poor body image, low self-esteem, and depressive symptoms; but also by life stage, cultural factors, delayed diagnosis, and inadequate education and information provision by healthcare professionals (Hollinrake et al., 2007; Deeks et al., 2011; Dokras et al., 2018). Several of these factors are beyond the reach of PA and exercise.

The Role of Exercise and Physical Activity on Body Image in Women with PCOS

Body image is typically defined as the way we feel, think about, and view our bodies including their appearance. For women with PCOS, several characteristics of the disorder, such as hirsutism, acne, and obesity, have potential to deeply undermine women's self-esteem, self-image, and self-worth which can have a significant negative influence on body satisfaction and body image (Bazarganipour et al., 2013). This can also affect perception of feminine identity (Dashti et al., 2016) and impact women's social lives, including sexuality, intimacy, and relationships (Pfister & Rømer, 2017). Generally, women with PCOS

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feel less physically attractive, healthy, or physically fit and are less satisfied with their body size and appearance, and this negative body image is associated with depression and anxiety (Teede et al., 2018). Hirsutism and increased weight most markedly negatively impact body image and quality of life (Dawber, 2005; Trent et al., 2005). Furthermore, infertile and hirsute women with PCOS have lower body satisfaction than non-infertile women and non-hirsute women with PCOS (Bazarganipour et al., 2013).

In a small, non-randomised pilot study, Liao et al. (2008) investigated the effects of a low-cost self-directed walking intervention on body image distress in overweight and obese women with PCOS. Distress with body size was highly prevalent for the overall sample. However, for women that completed the exercise programme, a significant reduction in body image recorded via the Body Dysmorphic Disorder Examination–Self-Report (BDDE–SR) questionnaire was reported after six months. Regrettably, only 34% of the original volunteers completed the programme which highlights the challenge of engaging and retaining people in exercise interventions. In a similar study, Kogure et al. (2020) randomly allocated 87 women with PCOS to 16 weeks of either continuous or intermittent aerobic exercise to assess the effects on body image, compared to a control group. In this study, to capture the multidimensional nature of body image, both cognitive-affective (attitudinal) and perceptual dimensions were assessed using the Body Shape Questionnaire (BSQ) and Figure Rating Scale (FRS), respectively. At follow-up, women in the two exercise conditions reported improved scores for the cognitive-affective dimension, but not the perceptive dimension, of body image. These results concur with those of Liao et al. (2018), since the BDDE–SR used in their study is similar to the BSQ (Jorge et al., 2008).

It has been suggested that the cognitive-affective dimension of body image responds positively to exercise interventions because engagement might increase women's sense of self-efficacy, encouraging them to focus more on the functionality of their body instead of its appearance (Alleva et al., 2015). It is conceivable that no effect in the perceptual dimension of body image was found because the FRS is limited to figure classification, circumventing feelings of distress about body image, which is typically positively associated with

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BMI (Zamani Sani et al., 2016). As recommended by Teede et al. (2018), given that negative body image in women with PCOS can result in increased depression and poorer HRQoL, body image should be considered as part of a comprehensive assessment and management plan to address both psychological considerations such as self-esteem and self-acceptance, as well as physical characteristics of the disorder such as hirsutism and obesity.

Broader Perspectives of Psychological Wellbeing and Health in Women with PCOS

We have discussed the impact of PCOS on depression, anxiety, some HRQoL outcomes, and body image. In doing so, most research innately considers negative aspects of mental health, by focusing on treating or preventing poor mental health, yet a nascent goal in mental health care is to focus on positive psychological wellbeing (PWB) (Weiss et al., 2016). For example, research with patients with mild to moderate psychological distress (Fledderus et al., 2010) and depressive symptoms (Korte et al., 2012) have used behavioural interventions that include PWB as an outcome measure. Similarly, resilience is another positive psychology approach and refers to the ability of individuals to face and overcome adversity adaptively and to implement strategies to cope with discomfort and adversity (Luthar et al., 2000; Tugade & Fredrickson, 2004; Campbell-Sills & Stein, 2007). As such, resilience is seen as a key factor in the well-being of individuals (Di Fabio & Palazzeschi, 2015). For future research it will be beneficial to include some broader perspectives of wellbeing involving women with PCOS. Two such perspectives are hedonia (subjective wellbeing) and eudaimonia (psychological wellbeing).

Hedonia is most often conceptualised as being made up of three key components: life satisfaction, positive affect, and negative affect (Diener, 1984). The theory is based around achieving maximum pleasure and experiencing minimum pain and placing stronger emphasis on positive emotional states to reach happiness (Kahneman et al., 1999). Eudaimonia is a lesser-known concept which draws on Aristotle's definition of a good life as one that is lived to the fullest

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potential in accordance with virtue or excellence. It places a stronger emphasis on meaning and purpose in life (Ryan et al., 2008), social relationships (Ryan & Deci, 2000), and challenging oneself to achieve growth (Compton et al., 1996).

Ryff and Singer (1996) have taken the convergent points from relevant philosophical theories and categorised them into six aspects: self-acceptance, purpose in life, personal growth, positive relations with others, environmental mastery, and autonomy. These six elements encompassing PWB have been used in wellbeing studies for elderly people with depressive symptoms (Afonso et al., 2011), outpatients with generalised anxiety disorder (Fava et al., 2005), and women with anorexia or bulimia (Stein et al., 2013). Research has shown that women living with PCOS express feelings of not being normal or good enough (Snyder, 2006; Pfister & Rømer, 2017), which might in turn effect their levels of self-acceptance. Furthermore, research has found women with PCOS express levels of guilt, disappointment, and self-blame (Snyder, 2006; Amiri et al., 2014; Martin et al., 2017), which may impact on self-acceptance, purpose in life, or personal growth. Other research has found that intimate relationships are negatively affected in women living with PCOS (Amiri et al., 2014; Kitzinger & Willmott, 2002), possibly limiting the positive support they get from the people close to them. Building on these findings, future research should explore how PWB might be impacted in women living with PCOS, and how this may further effect attitudes towards and participation in exercise and PA.

Physical and Physiological Benefits of Exercise

The Role of Exercise and Physical Activity in the Reduction of Cardiovascular Disease Risk in Women with PCOS

There is a graded inverse association between PA and CVD, with risk reducing as PA behaviour increases (Carnethon, 2009). PA is well recognised for its protective benefit on cardiovascular health, both for

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those without current CVD and as secondary prevention in those with CVD (Lollgen et al., 2009; Moore et al., 2012; Piepoli et al., 2004; Sattelmair et al., 2011). There have been attempts to establish a dose-response relationship between PA behaviour and CVD, morbidity, and mortality. In general, evidence indicates that any activity is better than none, and more activity is better than some (Chief Medical Officer's [CMO], 2019). The largest benefits are seen in those moving from being physically inactive (i.e., not meeting PA guidelines) to regular PA, and subsequent increases provide significant but diminishing returns (Stewart et al., 2017).

Lollgen et al. (2009) conducted a meta-analysis of prospective cohort studies to establish relative risk of all-cause mortality across PA intensity categories. Their categories for the analysis included mildly active, moderately active, and highly active, but with no specific definition offered. Nonetheless, for women specifically, the relative risk compared to the mildly active groups were 0.76 (95% confidence interval [CI]: 0.66, 0.89) for the moderately active group, with a further reduction to 0.69 (95% CI: 0.54, 0.89) in the highly active group, indicating additional benefits for increased PA behaviour. This effect was larger in women than in men. However, the authors indicated that PA in their study referred to leisure-time PA. PA undertaken as part of work or commuting was not considered, excluding participants from certain categories based on leisure time only. Additionally, PA behaviour was self-reported according to questionnaires (not standardised across studies) and this presents another issue regarding the measurement of PA in research studies. Not only might there be issues with accuracy of self-reports, but different questionnaires vary in validity and use of definitions, calling into question the heterogeneity of the meta-analysis.

Moore et al. (2012) conducted a meta-analysis of six prospective cohort studies (n = 654,827) to establish years of life gained, after age 40 years, across various levels of PA from low to high. Compared to no leisure time PA, hazard ratios for mortality were 0.81 (95% CI: 0.79, 0.83) for low levels of activity, 0.68 (95% CI: 0.66, 0.69) for levels at or just above the minimum level recommended by guidelines (150 min per week of moderate intensity PA), and 0.61 (95% CI: 0.59, 0.63) and 0.59 (95% CI: 0.57, 0.61) for two and three times the minimum

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recommended level, respectively. Thus, the results indicate a large reduction in risk when moving from low levels to the minimum recommended levels, with significant but diminishing effects for further activity above these. In addition, even low levels confer some health benefit, in line with recommendations that ‘some activity is better than none’.

Meeting PA guidelines for health presents a viable target for CVD risk reduction in women with PCOS. PA interventions have been reported to confer many benefits to the symptoms of PCOS, including lipid profile and insulin sensitivity (Harrison et al., 2011) and improved cardiorespiratory fitness.

The INTERHEART study found moderate to vigorous intensity PA to be one of nine lifestyle modifications that are protective against myocardial infarction (Yusef et al., 2004). Accordingly, there is compelling evidence that PA and exercise mitigates CVD risk factors in women with PCOS (Harrison et al., 2011; Kite et al., 2019; Patton et al., 2020), populations with dyslipidemia (Mann et al., 2014), populations with metabolic syndrome (Carroll & Dudfield, 2004; Katzmarzyk et al., 2003), and in healthy populations (Durstine et al., 2001). However, in relation to PCOS, some studies have produced inconsistent results with respect to the effectiveness of exercise only, without any additional dietary or pharmacological interventions, in improving biomarkers of CVD risk. This is particularly true regarding lipid profile (Hutchison et al., 2011), and inflammation (Beavers et al., 2010).

Longer duration exercise interventions (i.e., >20 weeks) are associated with improved lipid profile, and the reversal of metabolic syndrome in healthy populations (Katyzmarzyk et al., 2003; Carroll & Dudfield, 2004; Halverstadt et al., 2007). This might account for some of the discrepancy in PCOS research, with exercise interventions typically ranging from eight to 24 weeks in duration. PCOS studies with longer intervention durations have found improvements in very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) (Brown et al., 2009), whereas shorter interventions have found no change in low-density lipoprotein (LDL) and HDL, despite improvements in triglycerides (TG) and cardiorespiratory fitness (Hutchison et al., 2011).

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The Role of Exercise and Physical Activity in Weight Management Related Outcomes in Women with PCOS

Exercise interventions for 12-weeks, three sessions per week, can promote weight loss and reductions in BMI in women with PCOS (Hutchison et al., 2011). These changes are typically associated with a reduction in waist-to-hip ratio (WHR) or waist circumference (WC), indicating a decrease in abdominal obesity. Waist circumference and WHR may be a better indicator of health than BMI alone because of its association with other CVD risk factors, such as impaired glucose metabolism (Yusef et al., 2004; Teede et al., 2006).

While changes to BMI and WC seem to be more effectively reduced with combined exercise and dietary interventions in comparison to dietary intervention alone, weight loss is still achievable in shorter exercise-only interventions (Harrison et al., 2011). However, the amount of weight lost seems to be proportionately related to duration of the intervention (Hutchison et al., 2011). Longer duration (20 weeks or more) may be the key to promote greater weight loss, irrespective of type and frequency of exercise (Thomson et al., 2008).

The Role of Exercise and Physical Activity in the Reduction of Blood Pressure in Women with PCOS

Hypertension is one of the key characteristics of metabolic syndrome, and there is an inverse relationship between blood pressure and insulin sensitivity (Carroll & Dudfield, 2004). Evidence supports the role of exercise as treatment for hypertension, with exercise training decreasing blood pressure in around 75% of hypertensive adults, with a more pronounced effect in women (Hagberg et al., 2000).

In women with PCOS, the results are less clear with some studies finding no statistically significant improvements in systolic blood pressure (SBP) or diastolic blood pressure (DBP) in exercise interventions from 12 to 24 weeks (Giallauria et al., 2008; Brown et al., 2009), while others have found small, but clinically meaningful, improvements in SBP with exercise or exercise in combination with dietary intervention (Vigorito et al., 2007; Thomson et al., 2008). These

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conflicting results may be due to the wide range of phenotypes possible under the PCOS diagnostic criteria. Indeed, prevalence of hypertension in PCOS is reported to be between 5.5-12% (Ben Salem Hachmi et al., 2006; Joham et al., 2015) and as such many PCOS participants might be normo-tensive.

The Role of Exercise and Physical Activity in Improving Insulin Metabolism in Women with PCOS

There is much evidence to support the role of exercise in improving insulin metabolism. PCOS related research supports the role of exercise in improving insulin sensitivity immediately after an acute bout of exercise (Aye et al., 2018), but also in the long-term with exercise interventions from three months (Giallauria et al., 2008; Vigorito et al., 2007) to 20 or more weeks (Palomba et al., 2008; Thompson et al., 2009). This tentatively includes resistance training as well as aerobic exercise (Patton et al., 2020). Insulin resistance has been linked to abdominal obesity, hypertension, the development of type II diabetes mellitus (T2D) (Teede et al., 2006), dyslipidaemia, and inflammation (Zhou et al., 2014), meaning it is a key indicator of CVD risk in women with PCOS, where the prevalence of insulin resistance is up to 80% (Hutchison et al., 2011), independent of body weight.

Previous inconsistency in results could be due to intervention intensity. A recent review (Patton et al., 2020) of 20 studies investigated the impact of exercise interventions on PCOS and excluded any concurrent drug therapies. The authors concluded that exercise interventions from 10 weeks, involving 120 min/week of vigorous intensity exercise (60-85% maximal oxygen uptake [VO2 max]), were likely to result in greater improvements in cardiometabolic outcomes including homeostatic model assessment of insulin resistance (HOMA-IR), free androgen index, WC, and BMI, compared to moderate intensity exercise (40-60% VO2 max). Typically, previous studies have mainly focused on moderate-intensity exercise.

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Thus, while there is a need to introduce deconditioned individuals to exercise carefully, gradually increasing intensity above 60% of VO2 max may optimise health outcomes.

The Role of Exercise and Physical Activity on Reproductive Function in Women with PCOS

Several studies have explored the impact of PA and exercise interventions on reproductive function, with results indicating improvements in menstrual and/or ovulation frequency following exercise in comparison to diet or control groups (Vigorito et al., 2007; Palomba et al., 2008; Thomson et al., 2008). These improvements included a change from non-ovulatory to ovulatory cycles, restoration of cycle regularity, and improvement in inter-cycle variation (Harrison et al., 2011) indicating that exercise may be more beneficial to reproductive function than caloric restriction alone.

Evidence suggests that the pregnancy rate among women with PCOS undertaking an exercise intervention is 35% (Palomba et al., 2008), with pregnancy being a common reason for drop-out amongst participants with PCOS in exercise trials (Pericleous & Stephanides, 2018). It has been noted that lifestyle modification for infertile women with overweight or obesity and PCOS is a cost-effective solution for those women wishing to conceive, either as a primary intervention or in conjunction with fertility treatment (Mahoney, 2014). This suggests that women with PCOS presenting with reduced fertility could benefit from specific advice regarding exercise and PA programmes.

Enhanced insulin sensitivity underpins the mechanisms of how exercise restores reproductive function (Harrison et al., 2011). Reducing hyperinsulinemia decreases ovarian steroidogenesis and increases sex hormone binding globulin (SHBG), and the resulting return to a normo-androgenic environment may restore sensitivity of the gonadotropin-releasing hormone (GnRH) pulse activator to steroid inhibition of luteinising hormone (LH). Subsequently, decreased levels of LH and androgens may halt the excessive recruitment of antral follicles, allowing a dominant follicle to mature, eventually leading to ovulation.

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The Role of Exercise and Physical Activity in Improving Cardiorespiratory Fitness in Women with PCOS

Studies analysing PA behaviour and CVD risk tend to rely on self-reported data from questionnaires or activity logs which have limitations related to social desirability, bias, objectivity, recall, and accuracy. However, evidence indicates that cardiorespiratory fitness (CRF), measured by exercise-testing, are inversely associated with risk of all-cause mortality, independent of other CVD risk factors (Blair et al., 1989; Kodama et al., 2009; Mora et al., 2003). High CRF has been shown to substantially reduce, and in some cases eliminate, the higher risk of mortality associated with obesity (Lee et al., 1999; Stevens et al., 2002).

CRF is an objective indicator of habitual PA, and the mechanisms that link higher CRF to reduced mortality appear to be reflective of this. That is, higher CRF is associated with improved insulin sensitivity, blood lipid and lipoprotein profile, body composition, inflammation, blood pressure, and the autonomic nervous system (Lee et al., 2010). These improvements are all seen in those undertaking regular PA (Richter & Hargreaves, 2013; Stanford & Goodyear, 2014; Zhou et al., 2014; Soares-Miranda et al., 2016) Thus, high PA behaviour and greater CRF mitigate CVD risk. Measuring CRF should be utilised in a clinical setting to stratify risk and make important recommendations for disease prevention (Lee et al., 2010). It could also be used as an objective indicator for women with PCOS in determining the success of any exercise or PA programme.

Translating Evidence into Practice: Exercise Programming

While a single, unifying theory of the cause of PCOS is yet to be found, the main theories for the pathophysiology of PCOS include primary disordered gonadotropin secretion, primary ovarian and adrenal hyperandrogenism, and primary insulin resistance. Whichever the primary cause may be, exercise has been shown to play a role in

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normalising symptoms associated with each suggested aetiology. The current research outlined in this chapter provides compelling evidence that exercise can be used to alleviate or mitigate many of the cardiovascular, metabolic, reproductive, and psychological aberrations that are associated with PCOS.

An optimal dose-response relationship for exercise in PCOS might not be feasible because of the highly individualised characteristics of the disorder. Indeed, the Androgen Excess and PCOS (AE-PCOS) Society suggests that individualised exercise programmes may improve compliance and suggest group or home-based exercise (Wild et al., 2010). International guidelines for PCOS suggest at least 150 minutes of PA per week (Teede et al., 2011). This is in line with current UK PA guidelines for adults aged 19-64 years, and this should form the basis of any clinician or healthcare professional prescription. Most research examining the effects of exercise on PCOS symptoms focuses on aerobic activities such as walking, jogging, running, or cycling (Benham et al., 2018; Domecq et al., 2013; Harrison et al., 2011). For example, many of the benefits associated with exercise can be obtained by brisk walking, defined as faster than normal walking but at a pace that could be sustained for at least 20 minutes, and this is also the mode suggested by the AE-PCOS Society (Liao et al., 2008; Wild et al., 2010).

Metabolic improvements are possible in as little as 12-weeks (Hutchison et al., 2011). However, if weight-loss and/or improvement to lipid profile is also recommended, women with PCOS should undertake exercise programmes of longer duration (20 or more weeks), and consider the inclusion of a dietary component to achieve the best results, regardless of type or frequency of the exercise (Brown et al., 2009; Carroll & Dudfield, 2004; Katzmarzyk et al., 2003; Thomson et al., 2009).

The benefits of higher-intensity exercise (90-100% VO2 max) is less well-documented. However, positive improvements to insulin metabolism have been shown with high-intensity interval training sessions in women with PCOS (Harrison et al., 2012; Hutchison et al., 2011). In addition, resistance training is a mode of exercise that, in addition to its effectiveness in treating insulin resistance, may also decrease the loss of fat free mass (FFM) and increase lean body mass,

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whilst simultaneously reducing WC (Cheema et al., 2014; Vizza et al., 2016). This is a particularly important consideration for older women at risk of sarcopenia (Walston, 2012).

Regardless, an effective exercise programme that is engaging and that women with PCOS will adhere to is one that is client-centred, offering a choice of modes that may suit a variety of women of different physical abilities and preferences. In addition, the presence and support of other people may be a contributing factor to the compliance of an exercise or PA programme, and group or supervised exercise sessions should also be considered in addition to solitary exercise (Conte et al., 2015).

Resistance Training: An Under Studied Modality

Although aerobic exercise has been the focus of most PA interventions in women with PCOS, the study of resistance training interventions is starting to become more prolific. Indeed, resistance training is shown to be effective in the management of metabolic diseases, including type 2 diabetes and obesity (Tessierras & Balady, 2009).

In women with PCOS, studies have provided inconclusive results due to differences in participants, training loads and regimens, and whether resistance training was studied in isolation or additive to dietary components and/or aerobic exercise (Pericleous & Stephanides, 2018). As such, the updated PCOS guidelines do not make specific reference to resistance exercise in PCOS but defer to current population recommendations of 150 minutes per week of moderate activity (or 75 minutes of vigorous activity) and muscle strengthening activities on two non-consecutive days per week (Teede et al., 2018).

Progressive resistance training (PRT) may improve body composition and metabolic health in women with PCOS. Kogure et al. (2018) conducted a case-control study of a 16-week progressive PRT programme, performed three times per week for one hour. In total, 97 women completed the protocol (45 in the PCOS group and 52 in the non-PCOS group). The outcomes included biochemical measurements

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of testosterone and its intermediates, body composition and hypertrophy indicators, and muscular strength. Their results indicated that PRT significantly improved hyperandrogenism and glycaemia, increased muscular strength and lean body mass, and reduced body fat percentage in both the PCOS and non-PCOS groups compared to baseline. Improvements in muscular strength were observed from eight weeks, but changes in body composition were not significant before the 16-week measurement point. However, adherence to the protocol was 46% in the PCOS group and 54% in the control group, and participants only needed to complete a minimum of 20% of the sessions to remain in the study. Thus, low adherence may have attenuated results.

Of note, the authors used measures of FFM rather than body mass measurements to demonstrate changes in body composition. This is useful because muscle hypertrophy and increases in lean body mass may increase BMI, but the composition of such weight gain is more informative; for example, an increase in skeletal muscle size and quality is associated with increased insulin sensitivity and glucose tolerance, as well as increasing metabolic rate and the mobilisation of visceral adipose tissue in the abdominal region (Tresierras & Balady, 2009). Indeed, a recent systematic review and meta-analysis concluded that resistance training interventions in PCOS lead to increases in BMI, but reductions in WC, potentially indicating an increase in FFM and a reduction in visceral adipose tissue (Kite et al., 2019).

There are several RCTs investigating the effects of a resistance training intervention in comparison to other exercise modalities or control. Almenning et al. (2015) conducted a three-arm parallel RCT to identify the effects of resistance training (RT) and high-intensity interval training (HIIT) primarily on insulin resistance. Thirty-one women with PCOS were randomised to either the resistance training group, the HIIT group, or a control group (where women were advised to meet the national guidelines of 150 min per week of moderate intensity activity). The sample size was small but powered to detect significant changes in HOMA-IR; thus, other variables may have been underpowered. The participants engaged in 10-weeks of training, three times per week. Compliance was high, with participants attending 87% and 90% of the RT and HIIT sessions, respectively. The results indicated that HOMA-

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IR was significantly improved in the HIIT group only compared to baseline and the control group. However, in the RT group, percentage of body fat significantly decreased (-1.6% [95% CI: -2.5, -0.7]) and FFM significantly increased (1.2 kg [95% CI: 0.4, 2.1]) compared to baseline, despite no changes in BMI or WC. This consolidates previous research that suggests RT can be effective at modifying body composition without absolute weight loss. Further, the women in the study were not necessarily overweight, with the mean BMI of the RT group being 27.1 kg/m2. This suggests that lean or minimally overweight women with PCOS can still benefit from the use of RT to alter body composition without weight loss per se.

Vizza et al. (2016) conducted an RCT to determine the feasibility of an intervention involving a PRT group or a usual-care (control) group. The PRT involved two supervised sessions per week of machine-based and functional exercises, and two home-based (unsupervised) sessions of low intensity calisthenics. The study had a very small number of participants, further compounded by a high withdrawal rate. Subsequently, only six women completed in the PRT group and four in the control group. Nonetheless, in the PRT group, body weight, BMI, lean mass, and FFM were significantly increased compared to the control group, accompanied by significant decreases in WC. These results may further indicate the efficacy of RT in modifying body composition, but the limitation of the study as an unpowered feasibility trial (that is, its primary aim is to ascertain if a full-scale intervention is possible) must be considered when interpreting these results.

The effects of RT only on reproductive function are unclear. There are insufficient studies that examine the impact of RT in women with PCOS further highlighting the need for clear guidelines (Pericleous & Stephanides, 2018). PCOS guidelines currently make no specific recommendation regarding PRT, only deferring to general PA guidelines that refer to ‘muscle strengthening activities two times per week’ (Teede et al., 2018). However, the role of PRT in PCOS, particularly regarding body composition, appears promising. More specific guidelines related to exercises (isolated versus compound exercises) and training load (% of 1 repetition maximum, and repetitions/sets) are needed.

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Sedentary Behaviour Must be Considered

In the last decade research has shown the impact of sedentary behaviour on metabolic health. It is important to highlight, as per the definitions earlier in this chapter, that physical inactivity and sedentary behaviour are not the same thing. It is therefore entirely possible for an individual to be classed as physically active (because they meet PA guidelines for health) but spend most of their time sedentary. Indeed, in order to meet the UK physical activity guidelines, only 2% of one's time each day needs to be spent engaging in at least moderate intensity PA; the other 98% can be spent either sedentary or engaging in very light intensity activity (van der Ploeg & Hillson, 2017). This has given rise to the 'Active Couch Potato' phenomenon (Owen et al., 2010).

The negative impacts of excessive sedentary behaviour, even for those who are physically active, have begun to emerge. Sedentary behaviour and exercise, rather than being on a continuum, appear to be distinct behaviours with distinct physiologies; the cellular and molecular responses associated with each are qualitatively different (Hamilton et al., 2007). That is to say that although one can boost health with regular exercise, one can still be affected by the distinct cellular processes associated with too much sitting. These effects appear to be characterised by metabolic alterations commonly seen in diabetes and atherosclerosis (Hamilton et al., 2007). Indeed, television viewing time has been positively associated with abnormal glucose metabolism and the metabolic syndrome (Owen et al., 2010). Importantly, these effects persist even after adjustment for sustained moderate-to-vigorous activity, highlighting the deleterious effects of prolonged sedentary behaviour independent of the protective effects of regular PA (Owen et al., 2010).

Given the diminishing returns from continually increasing PA behaviour, the solution may not be that physically active persons should necessarily exercise 'more'. Rather, the shift in focus to reducing sedentary behaviours focuses on what can be done in non-exercise time (most of one's waking time) to target CVD risk. Focusing here may provide a different or additional option for improving cardiometabolic health: that is, light-intensity activity. Interrupting sitting with short breaks of low-intensity PA, such as walking slowly for several

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minutes per each 20-30 minutes of sitting, have been shown to improve glucose and insulin metabolism throughout the day (Dempsey et al., 2017; Dunstan et al., 2012). Critically, this is despite such light-intensity activity not contributing toward the 150 min per week moderate intensity PA guideline. Thus, this is potentially a valuable public health target because in the UK it is estimated that 27% of adults engage in less than 30 minutes of moderate or vigorous intensity PA per week (NHS Digital, 2019). Those that do not meet the PA guidelines and spend at least eight hours per day sitting are most at risk of CVD (Stamatakis et al., 2019). Thus, for people who are less inclined or able to engage in moderate or vigorous intensity PA, messaging that focuses on the importance of light-intensity PA (to break up sedentary behaviours) may be valuable for reducing CVD risk.

Indeed, while CVD risk over time in those who do not exercise cannot logically increase further due to exercise deficiency, it still has the potential to increase due to the distinct mechanisms of sedentary behaviours (Hamilton et al., 2007). Guidelines should therefore strive to make clear that in terms of PA, any non-exercise or light-intensity PA is better than none (Piepoli et al., 2016). UK guidelines have been recently updated to emphasise that light-intensity PA should also be undertaken to break-up sedentary periods (although there are no specific guidelines on how much or how often) (CMO, 2019), and this may go some way to stating the importance of light-intensity PA. In addition, for active individuals, including this type of PA may provide further CVD protection via distinct mechanisms in addition to those conferred by moderate or vigorous PA.

A limitation to exercise intervention studies in PCOS is uncontrolled or unmeasured sedentary behaviours. The 2018 PCOS guidelines (Teede et al., 2018) recommend that as well as encouraging PA, clinicians should emphasise minimised sedentary time for greater health-benefits. PA and exercise have been shown to improve insulin metabolism while sedentary behaviours are distinctly antagonist. Thus, it is possible that even those complying with an exercise intervention are spending much of their non-exercise time sedentary. The physiological impact caused by this could well affect results, with effects of exercise interventions potentially being dampened.

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Measurement of sedentary behaviours can be done via self-report using diaries, logs, questionnaires (such as the International Physical Activity Questionnaire [IPAQ]) or recall interviews. They can also be measured using worn devices such as accelerometers, inclinometers, pedometers, and heart-rate monitors. The latter tend to be more accurate but may be cost prohibitive, whereas self-reported measures are cheaper and easier to apply but tend to underestimate true sedentary behaviour (Prince et al., 2020). A recent systematic review indicated that multi-item questionnaires that ask more than one question about sedentary behaviours (such as the IPAQ long-form, which asks questions about sitting time, work time, and motorised travel time) provide data comparable to that collected by devices (Prince et al., 2020) and may be an affordable option.

There have also been no trials investigating the effects of (minimising) sedentary behaviour on CVD risk in women with PCOS, either in comparison to structured exercise or otherwise. Studies utilising devices and/or fitness app-based measures of sedentary behaviour and PA in an intervention may shed light on the impact of sedentary behaviours on CVD risk in PCOS. Indeed, the 2018 PCOS guidelines (Teede et al., 2018) recommend the use of fitness tracking devices and technology to self-monitor sedentary behaviours and PA via step count and other metrics. This can be done by most via mobile-phone, where relevant freely available apps, referred to as ‘mHealth interventions’, have been shown to be effective in reducing sedentary behaviours (Buckingham et al., 2019; Direito et al., 2017).

Since women with PCOS already display increased CVD risk factors and alterations in metabolic profile, sedentary behaviour may therefore be a further exacerbating factor. This presents an additional target for reducing CVD risk in women with PCOS; as well as partaking in regular PA, sedentary behaviours should also be reduced. At the present time, no studies have examined the impact of sedentary behaviour (and minimising this) on the metabolic and cardiovascular profile of PCOS.

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Practical Considerations for Exercise Prescription in Women with PCOS

When prescribing physical activity or exercise, below are some of the key considerations to keep in mind to maximise adherence to an exercise intervention based on the authors' experience of working with women living with PCOS:

1. Consider that women living with PCOS might have issues or anxieties surrounding body-image and self-esteem. As such, individual exercise sessions or small groups (potentially women only) within private facilities may be more effective than large, publicly accessible gym spaces.
2. Women should be informed of the benefits of exercise and PA even in the absence of weight loss, such as improved cardiovascular and metabolic health and increases in mental health and wellbeing (although it should be understood that weight loss might a strong driving factor for women particularly if they need to achieve BMI targets to be eligible for fertility treatment).
3. Explain how different types of exercise may affect PCOS symptoms (e.g., insulin resistance, hormone regulation, weight loss, cardiovascular fitness, mood swings, depression).
4. Enjoyment should be a key tenet of any PA or exercise intervention; try to ask the client about previous exercise modes or activities they have enjoyed and implement these.
5. Self-acceptance may affect how women value their body and self. This might create a sense of shame, blame, or guilt. Ensure that exercise is not seen as a duty, chore, or punishment for having PCOS.
6. Personal growth can be a driving factor for trying new types of activity and learning new skills. Purpose in life may improve motivation when goals are linked to personal values.
7. Environmental mastery assists the creation of suitable situations in which to enjoy and benefit from exercise. Autonomy can enable decision-making to suit personal perspectives.

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8. Consistency is key. Encourage the avoidance of 'all or nothing' behaviour. An active lifestyle and exercise program needs to be enjoyable and fit around all other pressures of life.
9. Undertake individual fitness testing and assessment before commencement of the programme and use the results to set bespoke training thresholds for the client. This will avoid discomfort from over-exertion which may increase injury risk and impact adherence possibly leading to drop out. However, the benefit of doing this should be judged against the likelihood that it might be seen as unpleasant or intimidating for many women with PCOS (focusing on sub-maximal testing to gain estimates of fitness might be more appropriate).
10. If individuals are not or have not been a habitual exerciser, begin training at low aerobic thresholds, i.e., 55-60% HR_{max} and increase the thresholds as the individual adapts to the demands of exercise and the programme progresses.
11. For extremely deconditioned individuals, intermittent activity with regular breaks may be more achievable at first.
12. If increased risk for CVD is present, such as hypertension and type 2 diabetes, close monitoring of heart rate and rate of perceived exertion (RPE) is recommended.
13. Be aware of the physical and psychological effects of medication and treatment procedures (especially fertility procedures).
14. PA and exercise should be seen as one part of the big picture. Consider physical, psychological, and spiritual aspects of life and implement healthy coping strategies where necessary.
15. Maintain a non-judgmental attitude and be supportive, encouraging, and empathetic. PCOS is heterogenous and complex impacting on all aspects of a women's daily life. See the person, not the syndrome.

CONCLUSION

The evidence reviewed in this chapter has highlighted the psychological, physical, and physiological benefits of an active lifestyle

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for women with PCOS. Overall, results from exercise studies appear to provide beneficial effects on a wide variety of PCOS symptoms including depression, quality of life, and a wide range of cardiovascular disease risk factors. Promoting exercise and PA is important in the management of the disorder (Teede et al., 2018). However, more research is needed to provide conclusive results to define effective types of exercise, as well as optimal duration and frequency. The addition of this research could lead to recommendations geared toward different symptoms or phenotypes and provide clearer guidance around the additional benefits for certain exercise or PA programmes over others. Research should also focus on positive psychological wellbeing and the effectiveness of exercise and PA strategies in "real-world" settings. Reduction of sedentary behaviour clearly attenuates CVD risk, and such conditions should be incorporated into PCOS lifestyle interventions to ascertain what benefits may be obtained in this population. Resistance training also warrants attention by researchers.

Key Points

- PCOS is a complex endocrinopathy affecting up to 20% of reproductive-aged women. It has a negative effect on health-related quality of life and psychological wellbeing and is associated with cardiometabolic and reproductive complications. Symptoms may be exacerbated by obesity.
- Insulin resistance is a key underpinning feature and exercise programmes that attenuate insulin resistance or hyperinsulinemia may be integral to improving associated symptoms.
- Research shows that exercise can improve reproductive function, cardiovascular and metabolic health, and mental well-being.
- Weight loss is not necessary for health improvements, and clinicians and healthcare professional should use the WHO guidelines as a basis to recommend PA.

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- Future research may be beneficial in indicating the efficacy of different exercise intensities, such as high-intensity exercise and progressive resistance training.
- Future research should also focus on positive psychological wellbeing and the effectiveness of exercise and PA strategies in "real world" settings.

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***Chapter* 11**

WORK IT OUT: EXERCISE AS AN ANTI-CANCER INTERVENTION

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ABSTRACT

Exercise or physical activity can be regarded as either an intervention for cancer prevention or an intervention for health promotion in people living with cancer. Here we discuss the effects of exercise and physical activity in reducing cancer risk and the clinical benefits for cancer patients and survivors. It is acknowledged that exercise can reduce the incidence of breast,

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colon and endometrial cancer, however the efficacy in reducing the incidence of some other cancer types such as prostate, ovarian, lung, gastric and haematological, is limited due to time limitation in randomized controlled studies and inaccurate measurements in observational studies. In general, it has been shown that exercise can prevent cancer cell proliferation, reduce oxidative damage, improve fat metabolism, reduce chronic inflammation and enhance immune functions. Research studies exploring the benefits of exercise in patients with breast and colon cancer have shown improved physical health and quality of life and a prolonged survival period. Likewise, exercise also provides good clinical outcomes for those living with prostate, endometrial, lung, gastric and hematological malignancies, although further research regarding exercise type and biological pathways are required. On the other hand, exercise may generate some adverse effects such as increased blood pressure, headache, muscle pain, physical accidents, severe discomfort, and dizziness amongst patients with cancer and survivors, especially those who are older and overweight or having hematological pathology following primary treatment with chemotherapy and/or radiation. As the benefits on clinical outcomes greatly outweigh the adverse effects, exercise for health in cancer patients and survivors should be recommended. However, considering the significant high rate of non-compliance to exercise in this cohort of individuals, the implementation of motivational strategies is vital otherwise any outcome benefits can be lost.

Keywords: exercise, physical activity, cancer patients, survivors, health promotion, physical health, psychological health, quality of life, biological pathway, biomarkers, adverse effects, motivation, exercise adherence

INTRODUCTION

Several decades of research in the area of exercise oncology has demonstrated the positive impact of physical exercise on cancer prevention, health promotion and cancer recurrence in a number of cancer type (Campbell et al. 2019; Moore et al. 2016; Schmitz et al. 2010). In people living with cancer, exercise has been shown to lower the mortality rate by up to 40% (Guinan, Hussey, and Connolly 2013). Therefore, clinical services should incorporatephysical activity

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promotion in patients and survivors during their follow-up period (Parker, Arlinghaus, and Johnston 2018). Furthermore, evidence shows that adult survivors of childhood cancers, who participate in continuous exercise for more than 8 years have a longer lifespan (Scott et al. 2018). The benefits of intentionalexercise have been reported in people living with a number of specific types of cancer (Battaglini et al. 2014; Courneya, Jones, et al. 2008; Courneya et al. 2014). However incidental physical activity of moderate intensity such as walking, cycling and household chores can decrease the mortality rate in males with prostate cancer (Bonn et al. 2015). Likewise, women with breast cancer who engage in physical activity have positive outcomes with a significant reduction in diease-related mortality (Guinan, Connolly, and Hussey 2013). The main research gaps in this field are in the specifics around types of exercise - volume, mode, intensity and frequency (Schmitz et al. 2010).

In this chapter, we will discuss how exercise or physical activity can reduce the risk of cancers and improve the health outcomes of patients with cancer. More specifically, we will discuss the feasibility and safety of exercise in patients with the most common types of cancer, such as breast, colon and prostate, as well as some less common tumors and investigate how an active lifestyle can alter biological mechanisms resulting in improved health.

RUNNING FROM CANCER – EXERCISE AS A PREVENTATIVE STRATEGY

Maintaining an active lifestyle that involves regular exercise and physical activity has been shown to prevent cancers associated with modifiable risk factors (Platek et al. 2017). It was found that there is a dose-response relationship between the level of physical activity and cancer risk reduction, with a lower cancer incidence associated with vigorous exercise and long duration rather than with moderate intensity exercise of shorter duration (Hayes et al. 2009). Therefore, exercise recommendations for the general population to reduce cancer risk are one hour of moderate or half an hour of heavy intensity exercise daily (Winzer et al. 2011).

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Over the last three decades, the effects of introducing exercise on health outcomes of cancer patients have been categorized into two distinct phases within the cancer continuum: (1) before (pre-screening and screening) cancer diagnosis and (2) after cancer diagnosis (pre-treatment, treatment, survivorship and end of life) (Schmitz et al. 2010). In the pre-screening and screening periods the purpose of exercise in the general population is for cancer prevention (Schmitz et al. 2010). There is stronger and more convincing evidence linking physical activity to a reduction in risk of colon, breast and endometrial cancers with weaker associations in ovarian, prostate and lung malignancies (Friedenreich, Neilson, and Lynch 2010). There is insufficient evidence regarding the association in other malignancies such as hematological, cervical and gastric cancers (Friedenreich, Neilson, and Lynch 2010). However, a retrospective cohort study reported that sedentary lifestyle was directly correlated with the incidence of head and neck cancers (Platek et al. 2017).

Observational studies and randomized trials are valuable in testing how physical activity and exercise can prevent cancer, however both have limitations (McTiernan 2016). Observational studies are subject to measurement errors as most data analysis is reliant upon the participant's memory thus prone to recall bias and impacted by confounding factors such as age, race, socioeconomic status and dietary pattern (McTiernan 2016). Likewise, in randomized controlled studies there may be time limitations around when cancer incidence occurs (McTiernan 2016). Hence, surrogate outcomes or intermediate-scale testing of cancer pathways involving biomarkers should be included in randomized studies to help predict long-term cancer prevention after physical activity (McTiernan 2016).

There are several biological mechanisms explaining how exercise can prevent cancer cell proliferation. There is evidence to show that exercise can alter biological mechanisms that block cancer initiation and progression such as the reduction of oxidative damage within the cell, epigenetic modification, change in body weight and fat metabolism, altered growth factors and reproductive hormones, reduced chronic inflammation and improved anti-cancer immunity (Rogers et al. 2008).

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One possible biological pathway which can help cancer prevention is the adiposity modulatory effect (Friedenreich and Orenstein 2002). This refers to the reduction of abdominal fat with physical activity, which is associated with controlled blood glucose and improved insulin metabolism, and a decline in cancer risk (Friedenreich and Orenstein 2002). A randomized study of the impact of a one-year of endurance exercise intervention in postmenopausal women, revealed a reduction in body weight and abdominal fat alongside a reduced risk of breast cancer (Friedenreich, Woolcott, et al. 2011). Likewise, one year of moderate to high intensity aerobic exercise for sixty minutes per day resulted in a reduction in weight and intra-abdominal fat in both healthy male and female participants, enhanced insulin efficiency and a reduced risk of colon, breast and endometrial cancers (McTiernan et al. 2007). Several randomized controlled trials also reported reductions in the levels of cancer related biomarkers, such as serum insulin, leptin, adiponectin and estrogen (Campbell and McTiernan 2007). It was also found that the reduction in serum leptin and adiponectin were associated with increased insulin sensitivity after a year-long aerobic exercise regime in postmenopausal women, a predictor for breast cancer prevention (Friedenreich, Neilson, et al. 2011). Another year-long aerobic exercise intervention study showed significantly reduced estradiol but increased sex hormone binding globulin (SHBG) among postmenopausal women, which was also associated with a reduced breast cancer risk (Friedenreich et al. 2010).

High-intensity exercise training can facilitate natural killer cell (NK cell) anti-tumor cytotoxicity in healthy adults (Bigley and Simpson 2015). In mice, voluntary exercise results in NK cells mobilizing into the bloodstream in response to epinephrine and a reduction in inflammatory signaling from myeloid immune cells, inhibiting tumor growth (Hojman 2017). Exercise has also been shown to diminish the normal immune function deterioration seen with aging, subsequently reducing cancer incidence. A study in 2013 showed that there was an increase in innate (NK cell cytotoxic activity and monocytes) and adaptive (antigen presenting cells) immune activity after aerobic and resistant training in the elderly (Bigley et al. 2013).

There has been some investigation into the value of 'cancer pre-habilitation' and its effects on cancer outcomes. Silver and Baima

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(2013) define cancer pre-habilitation as the “process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient’s health to reduce the incidence and the severity of current and future impairments.” (p2) (Silver and Baima 2013). The benefits of cancer pre-habilitation include improvements in health outcomes, increased number of options for treatment, a decrease in hospital readmission and a reduction in the overall financial burden to both the healthcare system and the individual (Santa Mina et al. 2017). It is suggested that a ‘multi-modal’ approach, which incorporates both physical and psychological intervention, is preferable to optimize the beneficial effects. Physical exercise interventions, including aerobic and strength training prior to treatment, improved cardiovascular fitness and aided in a speedy recovery post treatment (Doyle et al. 2006; Carli et al. 2017). Psychological interventions, such as educating patients on stress management techniques prior to radical prostatectomy surgery, resulted in lower levels of mood disturbance pre-operatively and increased immune parameters post-surgically (Cohen et al. 2011).

In a meta-analysis study, it was noted that exercise prescription for cancer patients during treatment, cosisting of mild to moderate intensity, 3 to 5 times a week for a minimum of 20 minutes, of aerobic, weight or combined training likely reduced cancer-related fatigue (Velthuis et al. 2010). During cancer treatments, exercise also reduces adverse side effects such as thrombocytopenia, diarrhea and pain as well as reducing the hospital length of stay (Schmitz et al. 2010).

Stronger Outcomes – The Beneficial Effects of Exercise in Cancer

Exercise and Breast Cancer

With improvements in survival rate, there are now large numbers of breast cancer survivors worldwide, increasing the availability of research studies investigating associated breast cancer outcomes

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(Patterson et al. 2010). Many studies have demonstrated a correlation between regular exercise and the reduction of cancer recurrence and mortality rates, in both active patients and survivors, most likely due to the alteration in adiposity-related biomarkers and immune function (Pudkasam et al. 2017). Generally, exercise prescription as pre-habilitation in cancer patients before surgery can facilitate post-operative recovery and reduce mortality (Carli et al. 2017). Likewise, females with breast cancer who reported an active lifestyle or participated in an exercise trial before surgery, had a faster recovery and fewer complications in the post-operative period compared with sedentary patients (Santa Mina et al. 2017). Pre-habilitation programs involving arm exercises promote improved shoulder range of motion and reduce pain following breast surgery (Baima et al. 2017).

Exercise during treatment has also been shown to have beneficial effects. A randomized controlled study which implemented 18 weeks of supervised aerobic and resistance exercises during the early stages of chemotherapy treatment in breast cancer patients, revealed that physical fatigue was less than in the usual care group (Travier et al. 2015). A home-based walking program for breast cancer patients undergoing radiotherapy and chemotherapy was also reported as being effective in reducing fatigue scores compared with controls (Mock et al. 2001). Improvement in lean mass, body composition and body image were also reported in breast cancer patients undertaking weight training during chemotherapy (Schmitz et al. 2010).

A randomized controlled study illustrated the long-term beneficial effects of an 18-week supervised endurance and muscle strengthening exercise program during chemotherapy in patients with early stage breast or colon cancers (Witlox et al. 2018). The study showed that the program reduced the physical fatigue normally associated with chemotherapy treatment at 18 weeks (Witlox et al. 2018). A year-long prospective study identified a relationship between exercise participation and improved physical function with an associated improvement in quality of life (QoL) in early stage breast cancer survivors, upon completion of active cancer treatment (Pinto et al. 2002). A systematic review and meta-analysis reported an improvement in hazard ratio of 0.45 for mortality in breast cancer survivors at the early stage of disease who participated in the exercise

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program, compared with the control group (Falcetta et al. 2018). Exercise after breast cancer diagnosis can reduce cancer-related and overall mortality by approximately 30% and cancer recurrence by about 20% in postmenopausal women (Dieli-Conwright and Orozco 2015). The likely mechanism mediating these effects is a reduction in inflammatory processes and body fat, that occur as a response to exercise (Dieli-Conwright and Orozco 2015). A meta-analysis reported an inverse relationship between exercise volume and fasting blood insulin levels among female breast cancer survivors, a predictor for improved breast cancer clinical outcomes (Kang et al. 2016). Additionally, a 10-year longitudinal study posited that the reduction in insulin can decrease mortality in postmenopausal women with breast cancer (Borugian et al. 2004). A six-month program which combined moderate exercise and dietary control in obese patients in the early stages of breast cancer was shown to significantly reduce body weight and waist-hip ratio, resulting in decreased leptin and total blood cholesterol levels (Scott et al. 2013). These outcomes can contribute to improved health outcomes and longer survival periods (Scott et al. 2013). Another study showed that a four-month supervised resistance training program promoted an anti-inflammatory mediated effect against cancer recurrence by reducing the level of tumor necrosis factor-alpha (TNFα) in breast cancer survivors (Hagstrom et al. 2016).

Breast cancer patients undergoing chemotherapy or radiotherapy have been reported as being protected against the normal change in immune cell number (white blood cells, lymphocytes, helper T cells, cytotoxic T cell and natural killer cells) after a 12 week walking program (Kim, Shin, and Suk 2015). Breast cancer survivors who commenced a six month aerobic exercise program immediately following completion of their chemotherapy treatment, showed an enhancement in T-lymphocyte activation with an increased percentage of CD4+CD69+ T-cells (Hutnick et al. 2005) and a reduction in the period of neutropenia and thrombocytopenia (Schmidt et al. 2017). Additionally, 15 weeks of cycling, in post-menopausal breast cancer survivors, significantly increased the cytotoxic activity of NK cells (Fairey et al. 2005). However, the challenges around understanding the positive relationship between exercise and breast cancer requires a more in depth understanding in physical activity interventions, specifically the

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underpinning biological mechanisms (Jiralerspong and Goodwin 2016; Friedenreich and Cust 2008).

Exercise and Colon Cancer

The main breadth of research into the benefits of exercise in cancer pertains to breast cancer, however other studies report similar benefits in other cancer types such as colon cancer. Physical activity was shown to have an inverse association with the risk of colon cancer, though interestingly this was not consistent in rectal malignancy (Martínez 2005). Additionally, a systematic review found that physical activity resulted in protection against colon cancer in both men and women but again failed to have protective effects in rectal malignancy (Samad et al. 2005). A recent randomized controlled study concluded that there was a reduction in the numbers of colon cancer cells in vitro alongside increased levels of serum TNFα, interleukin-6 (IL-6) and interleukin-8 (IL-8) amongst colon cancer survivors following an acute high intensity interval exercise program (Devin et al. 2019). A cohort study noted that colon cancer survivors who were physically active had a reduction in mortality rate (Meyerhardt et al. 2009). However, this beneficial outcome was likely to occur in colon cancer survivors with particular subgroups of molecular markers (Meyerhardt et al. 2009). Biological mechanisms underpinning the protective effect of exercise may be changes in gastrointestinal-pancreatic hormones, improved gastrointestinal transit time, bile acid and prostaglandin secretion and immune function (Quadrilatero and Hoffman-Goetz 2003). Exercise can increase gastrointestinal peptide hormone levels and bowel movement during resting periods. As a result, carcinogen exposure time is shortened at the mucosal layer (Quadrilatero and Hoffman-Goetz 2003). Vigorous exercise also seems to increase prostaglandin (PG)F2α and decrease PG2 levels, increasing bowel motility which can prevent the development of colon carcinoma (Slattery 2004). A randomized controlled study in which colon cancer patients undertook an 18-week supervised aerobic exercise regime combining muscle strength training during chemotherapy, resulted in a decrease in their physical and mental fatigue (Van et al. 2016).

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A randomized controlled study investigated the feasibility of a 6-month endurance exercise program at either moderate (150 minutes weekly) or high (300 minutes weekly) volume in colon cancer survivors (Brown, Troxel, et al. 2018). The study highlighted that aerobic training at both moderate and high volumes can reduce endothelial cell-adhesion molecules (sICAM-1 and sVCAM-1), which are indicators of colon cancer metastasis (Brown, Troxel, et al. 2018). The same study also reported a reduction in fasting insulin levels and insulin resistance following completion of the exercise program, known predictors of positive colon cancer outcomes (Brown, Rickels, et al. 2018). Additionally, the reduction in sICAM-1 and insulin were associated with circulating tumor cells in colon cancer survivors in both the moderate and high volume exercise programs, again suggesting a decrease in metastatic behavior (Brown, Rhim, et al. 2018). A 3-year randomized controlled study that incorporated supervised exercise and behavioral change strategies, such as social support from a partner and self-monitoring, promoted long term physical activity engagement in colon cancer survivors (Courneya, Booth, et al. 2008). A four week pre-habilitation program of moderate aerobic and resistance training for 20 minutes, 3 times per week was shown to improve physical fitness in colorectal cancer patients before surgery (Chen et al. 2017). Of the patients who received pre-habilitation, 80% returned to baseline physical function at 8 weeks post-operation (Carli et al. 2017). They also reported reduced levels of fasting insulin and TNF-α but increased levels of adiponectin, insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 after 12 weeks of home-based physical activity, factors associated with good outcomes for colorectal cancer patients (Lee et al. 2013).

There is sufficient evidence to support the advantages of physical activity in cancer prevention and recurrence amongst people with colon cancer however, this is not the case in rectal cancer (Denlinger and Engstrom 2011). While, the evidence is not as significant, preoperative rectal cancer patients show improvement in cardiovascular fitness after 6 weeks of bike training (West et al. 2015). Rectal cancer patients undergoing chemotherapy and radiotherapy also reported a positive perception of their physical health and QoL after six weeks of supervised endurance exercise training (Morielli et al. 2016). Barriers to

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exercise adherence in these patients during treatment included diarrhea, fatigue and skin irritation (Morielli et al. 2016). A 6-week supervised aerobic exercise program for advanced stage rectal cancer survivors is reported to have enhanced physical and psychological well-being (Burke et al. 2013). Colorectal cancer survivors who have an active lifestyle are likely to have better QoL and physical health than those with a sedentary lifestyle (Peddle, Au, and Courneya 2008). Therefore there is a recommendation that older adults increase the amount of physical activity to reduce the risk of colorectal cancer (Chao et al. 2004).

Exercise and Prostate Cancer

Prostate cancer is a considerable cause of morbidity and mortality in men (Culp et al. 2020). Exercise has been recommended for reducing prostate cancer risk and increasing health promotion amongst men with prostate cancer (Torti and Matheson 2004). The effect of exercise in reducing prostate cancer development is suggested to be via mechanisms of alteration to adiposity, hormone and immune related biomarkers (Torti and Matheson 2004). A systematic review highlighted the feasibility of exercise programs in prostate cancer patients. Exercise contributed to many positive outcomes including improved physical fitness, body composition and bone density (Neil-Sztramko et al. 2019). Three months of supervised aerobic exercise combined with resistance training in prostate cancer patients receiving the standard androgen-deprivation therapy (ADT), reported improvements in physical fitness and mental health alongside a reduction in body fat (Cormie et al. 2015). One month of treadmill running in mice with induced prostate cancer resulted in increases in left ventricular wall thickness and stroke volume, hypothesized to reduce the fatigue usually present in prostate cancer patients and survivors (Baumfalk et al. 2019). Exercise can reduce common side effects of ADT such as fatigue, obesity, sexual dysfunction and reduced bone density (Campos et al. 2018). In prostate cancer patients undergoing ADT, aerobic exercise programs plus strength training, resulted in a reduction in fatigue (Taaffe et al. 2017), improved cardiorespiratory fitness and

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body composition (Wall et al. 2017) and an attenuation of bone mineral density loss in the lumbar spine and the neck of the femur (Newton et al. 2019). However, future studies are needed to confirm the types of exercise intervention that are most effective as well as clarification on the biological mechanisms and endpoints which are contributing to positive outcomes in prostate cancer patients (Galvão et al. 2016).

Exercise and Other Cancers

The majority of research into exercise oncology through the late 1900's, had centered around common cancers such as breast, colorectal and prostate cancer prompting a call for more recent investigation into rarer malignancies (Karvinen et al. 2007). A systematic review on the impact of exercise therapy in cancer oncology suggested that moderate to vigorous exercise is helpful across heterogenous types of cancer throughout the cancer continuum before, during and after therapy (Stout et al. 2017).

Given that common risk factors for endometrial cancer are inactive lifestyle and high body mass index (BMI), it could be deemed reasonable to assume that endometrial cancer survivors would benefit from regular physical activity or exercise (Basen-Engquist et al. 2013). Some evidence supports this assumption with an improvement in the reported pain and anxiety-related QoL in endometrial cancer survivors following completion of a six-month program consisting of home-based exercise and telephone counselling (Song et al. 2017). Another body of evidence showed a reduction in waist circumference and improvement in QoL in obese endometrial cancer survivors following a 12-week home-based walking program (Rossi et al. 2016). Two further studies showed improvements in general health, pain and somatic symptoms and perception of sexual health in endometrial cancer survivors following a six-month home-based moderate intensity exercise program (one study also included regular telephone counselling sessions) (Armbruster et al. 2016; Robertson et al. 2019).

It is reported that the majority of lung cancer patients have inactive lifestyles and exercise intolerance (Bade et al. 2015). Even though physical activity promotion in lung cancer is challenging, survivors are

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motivated to perform exercise immediately after surgery, as well as after adjuvant chemotherapy (Twomey, Bebb, and Culos-Reed 2018). A study which investigated whether patients with late-stage lung cancer were receptive to physical activity rehabilitation services revealed that only 30 percent were receptive. The reasons given by the remaining patients as to why they were not receptive centered around poor time management, less prioritization and lack of understanding of the beneficial effects of rehabilitation (Cheville et al. 2017). Evidence-based studies report that exercise can improve lung capacity, exercise tolerance and QoL in these populations (Twomey, Bebb, and Culos-Reed 2018; Bade et al. 2015). A cohort study illustrated a lowering in mortality of lung cancer patients who performed more than seven hours of weekly moderate to vigorous physical activity (Arem et al. 2014).

Participation in physical activity of moderate intensity is also suggested to reduce the risk of gastric carcinoma in both males and females (Wolin and Tuchman 2010). It is theorized that patients with gastrointestinal (GI) cancer have reduced morbidity after surgery, therefore pre-operative exercise therapy is one strategy for improved recovery during the post-operative phase in these patients (Vermillion et al. 2018). Gastric cancer patients undergoing cancer treatment show improved physical capacity and QoL after 3 to 8 months of moderate to high intensity supervised aerobic exercise (Heislein and Bonanno 2009). Patients with advanced gastric cancer are shown to have improved lean body mass and balance after 12 weeks of home-based moderate walking (Stuecher et al. 2019). Contrary to these findings, a three month randomized controlled trial in metastatic lung and gastrointestinal tract cancer patients demonstrated up to 75% exercise adherence to a designated exercise program in these individuals (Uster et al. 2018). However, these studies failed to show an improvement in patients' perception towards QoL indicators (Uster et al. 2018; Wiskemann et al. 2018).

It has been reported that low levels of physical activity are common in haematological cancer survivors. As a consequence, they may suffer from a deterioration of various health parameters (Wolin et al. 2010). However, a systematic review revealed the feasibility and safety of low to high intensity aerobic exercise in adults with acute leukemia, multiple myeloma and lymphoma (Battaglini 2010).

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Table 1. Positive outcomes regarding to the different types and duration of physical activity across various types of cancer continuum

Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
RCT (McTiernan et al. 2007)	One year supervised +home-based MVPA	General cancer prevention	40 to 75 year old men and women	Adiposity and body composition	- Decreased BW and BMI - Decreased waist and hip circumstance
Breast Cancer					
RCT (Friedenreich, Woolcott et al. 2011)	One year supervised +home-based MVPA	Breast cancer Prevention	50 to 74 year old postmenopausal women	Adiposity and body composition	- Increased aerobic fitness, decreased body weight, body fat and abdominal fat - Decreased waist and hip circumstance
RCT (Friedenreich, Neilson et al. 2011)	One year supervised +home-based MVPA	Breast cancer Prevention	50 to 74 year old, postmenopausal women	Adiposity and insulin	- Decreased serum insulin and leptin
RCT (Friedenreich et al. 2010)	One year supervised +home-based MVPA	Breast cancer Prevention	50 to 74 year old, postmenopausal women	Reproductive hormone	- Decreased oestradiol and free oestradiol - Increased sex hormone binding globulin
RCT (Travier et al. 2015)	18 weeks supervised aerobic and resistance exercise	During breast cancer treatment (chemotherapy)	25 to 75 year old breast cancer patients	Physical health, mental health and QoL	- Increased aerobic fitness and muscle strength

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Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
RCT (Mock et al. 2001)	6 weeks Home based walking	During breast cancer treatment (chemotherapy or radiotherapy)	52+ 9 year old breast cancer patients	Physical health, mental health and QoL	- Reduced fatigue and emotional distress - Increased functional ability and QoL
RCT (Witlox et al. 2018)	18 weeks supervised aerobic and resistance exercise	During breast and colon cancer treatment (chemotherapy or radiotherapy)	59.9 + 9 year old breast cancer and colon cancer patients	Physical health	- Decreased physical fatigue at 4 years post baseline
Single- armed experimental study (Kim et al. 2015)	12-week walking exercise program	During breast cancer treatment (chemotherapy or radiotherapy)	47.8 ± 6.77 year old breast cancer patients	Adiposity and immune	- Reduced BW, BMI and percent body fat
Longitudinal Prospective Cohort study (Pinto et al. 2002)	The details of MVPA in participants over 12 months	After breast cancer treatment	57.5 + 13.2 year old breast cancer survivors	Physical function, Psychosocial health and QoL	- Improved physical health
Longitudinal Prospective Cohort study (Borugian et al. 2004)	The details of physical activity in participants over 10 years	After breast cancer treatment	54.5 + 11 year old breast cancer survivors	Insulin and reproductive hormone	- Higher serum insulin is associated with breast cancer mortality rate - Serum insulin is associated with BMI - Serum insulin is negatively associated with SHBG

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Table 1. (Continued)

Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
RCT (Scott et al. 2013)	24 weeks supervised exercise (aerobic and weight training)	After breast cancer treatment	55.7 + 9.5 year old breast cancer survivors with obesity	Adiposity and reproductive hormone	- Reduced BW and BMI - Reduced waist circumference and WHR - Change in BW and waist circumference is positively associated with change in leptin - Change in BW and waist circumference is negatively associated with change in SHBG
RCT (Hagstrom et al. 2016)	16 weeks supervised weight training	After breast cancer treatment	51.9 + 8.8 year old breast cancer survivors	Immune function and inflammatory	- Decreased TNF-α by NK cells and NKT cells
Non-RCT (Hutnick et al. 2005)	6 months supervised aerobic and resistance training	After breast cancer treatment	48.5 + 10.6 year old breast cancer survivors	Immune function	- Increased percentage of CD4+CD69+ T-helper cells
RCT (Fairey et al. 2005)	15 weeks moderate intensity of cycling	After breast cancer treatment	50 to 69 year old breast cancer survivors	Immune function	- Increased NK cell cytotoxic activity - Increased unstimulated [^{3}H]thymidine uptake by peripheral blood lymphocytes
Colon Cancer					

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Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
RCT (Van et al. 2016)	18 weeks supervised exercise program	During Colon cancer treatment (Chemotherapy)	58.1 + 10.3 year old male and female colon cancer patients	Physical and psychological health	- Reduced physical fatigue and general fatigue
RCT (Brown, Troxel et al. 2018)	6 months low to high aerobic exercise	After colon cancer treatment	56.5 + 10 year old male and female colon cancer survivors	Colon cancer metastasis	- Reduced endothelial cell-adhesion molecules (sICAM-1 and sVCAM-1)
RCT (Brown, Rickels et al. 2018)	6 months low to high aerobic exercise	After colon cancer treatment	49.1 to 63.3 year old male and female colon cancer survivors	Metabolic growth factors	- Reduced fasting insulin and insulin resistance
RCT (Brown, Rhim et al. 2018)	6 months low to high aerobic exercise	After colon cancer treatment	55.9 ± 9.3 year old male and female colon cancer survivors	Colon cancer recurrence	- Reduced circulating tumour cells
Non-RCT (Devin et al. 2019)	4 weeks high intensity interval exercise training	After colorectal cancer treatment	> 40 year old Male colorectal cancer survivors	Inflammatory and cell proliferation	- Increased IL-6, Il-8 and TNF-α after one bout of high intensity exercise training - Reduced colon cancer cell growth after one bout of high intensity exercise training

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Table 1. (Continued)

Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
					- Physical activity is associated with reduced colorectal cancer mortality rates
Two prospective Cohort studies (Meyerhardt et al. 2009)	Leisure activity was assessed every 2 years since 1986 to 2006	After colon cancer treatment	Median age 67.5 year old male and female colon cancer survivors	Immunohistochemistry and mortality rate	- Reduced tumours with expression of p27 - Reduced colon cancer–specific mortality and overall causes (by exercise at least 18 MET per week)
RCT (Lee et al. 2013)	12 weeks home-based moderate intensity physical activity	After colon cancer treatment	55 ± 12.94 year old male and female colon cancer survivors	Metabolic growth factors	- Reduced fasting insulin and TNF-α - Increased adiponectin, insulin growth factor-1 (IGF-1) and IGF binding protein-3
Rectal Cancer					
Non-RCT (West et al. 2015)	6 weeks exercise training program	Before rectal cancer operation	64 (45–82) year old males with T3–4/N+ resection margin threatened rectal cancer	Physical fitness	- Increased cardiovascular fitness (VO_2 peak)

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Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
A prospective single group study (Morielli et al. 2016)	6 weeks aerobic exercise sessions	During and after rectal cancer treatment (chemotherapy and radiotherapy)	57.5 +10.4 year old male and female rectal cancer patients	Health-related fitness	- Improved 6 minute walk test - Positive perception towards health
A longitudinal study (Burke et al. 2013)	6 weeks interval exercise training	Preoperative phase in advanced stage of rectal cancer	58.2 + 7.7 year old male and female rectal cancer patients	QoL	- Improved vitality, positive attitude, social connection and strong sense of purpose
Gastrointestinal Cancer					
A single -arm pilot study (Heislein and Bonanno 2009)	21 weeks progressive walking programs	During gastrointestinal cancer treatment	Gastrointestinal cancer patients (No age reported)	QoL and aerobic fitness	- Increased exercise capacity - Trend towards improved QOL.
RCT (Stuecher et al. 2019)	12 weeks of home-based walking exercise	During gastrointestinal cancer treatment (chemotherapy)	67.1 ± 7.8 year old male and female gastrointestinal cancer patients with advanced stage	Physical capacity	- Enhanced gait speed, body balance and lower extremities muscle strength - Increased lean body mass
Prostate Cancer					

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Table 1. (Continued)

Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
RCT (Cormie et al. 2015)	3 months supervised aerobic and resistance training	During prostate cancer treatment	69.6 ± 6.5 year old male prostate cancer patients undergoing androgen-deprivation therapy (ADT)	Body composition and physical health	- Increased lean mass - Decreased fat mass - Reduced cholesterol : HDL ratio - Reduced CRP - Improved physical fitness and QoL
RCT (Taaffe et al. 2017)	12 months supervised resistance exercise session	During prostate cancer treatment	68.9 ± 9.1 year old male prostate cancer patients undergoing ADT	Bone mineral density and cardiovascular capacity	- Reduced fatigue in impact loading + resistance training group at 6 months
RCT (Wall et al. 2017)	A 6-month aerobic and resistance exercise program	During prostate cancer treatment	69.1 ± 9.4 year old male prostate cancer patients undergoing ADT	Cardiovascular fitness and body composition	- Improved VO_2max - Improved fat oxidation and lean mass
RCT (Newton et al. 2019)	12 months impact loading resistance exercise	During prostate cancer treatment	68.7 ± 9.3 year old male prostate cancer patients undergoing ADT	Bone mineral density and muscle	- Improved BMD of spine and neck of femur - Increased appendicular skeletal muscle
Endometrial Cancer					

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Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
A secondary analysis of one-arm longitudinal study (Song et al. 2017)	6 months moderate intensity exercise	After endometrial cancer treatment	57.7 + 10.3 year old female endometrial cancer survivors	QoL	- Improved pain and anxiety related QoL
A single -armed pre-post study (Robertson et al. 2019)	6 months moderate-intensity walking	After endometrial cancer treatment	Female endometrial cancer survivors (No age reported)	QoL	- Improved role limitation due to physical health and general health
A secondary analysis of non-controlled, single-arm study (Armbruster et al. 2016)	6 months home-based exercise	After endometrial cancer treatment	58.2 + 9.7 year old female endometrial cancer survivors	Reproductive health	- Correlation between exercise and improved sexual health
Hematological Cancer					
A prospective cohort study (Arem et al. 2014)	Past 10 years MVPA was assessed between 1996-1997	Pre-diagnosis, cancer diagnosis and cancer death were observed	General males and females	Cancer caused mortality rate	- Reduced overall cancer related death with increased MVPA - 7 hours per day MVPA and death due to liver, colon, lung and non-Hodgkin's lymphoma

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Table 1. (Continued)

Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/Health	Positive surrogate or clinical outcomes
A single -arm study (Dimeo et al. 2003)	Walking on a treadmill during hospital admission for chemotherapy	During hematological cancer treatment (chemotherapy)	48 ± 15 year old male and female hematological cancer patients	Physical capacity	- No change in physical performance on submaximal exercise stress test. Decreased haemoglobin levels

Abbreviations: ADT, androgen-deprivation therapy; BMD, bone mineral density; BMI, body mass index; BW, body weight; CRP, C-reactive protein; HDL, high density lipoprotein; IGF, insulin growth factor; MET, metabolic equivalent of task; MVPA, moderate vigorous physical activity; NK, cell natural killer cell; NKT cell, natural killer T cell; QoL, quality of life; RCT, randomized controlled trial; SHBG, sex hormone binding globulin; TNF, tumour necrosis factor; VO_2, oxygen consumption; WHR, waist hip ratio.

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Moderate aerobic exercise in hematological cancer patients during a month of hospitalization for chemotherapy had no effect in physical performance even though their hemoglobin concentration levels decreased (Dimeo et al. 2003). The positive outcomes of physical activity and exercise programs, by different types and duration, across the cancer continuum, are summarized in Table 1.

MORE PAIN OR MORE GAIN? ADVERSE EFFECTS OF EXERCISE IN CANCER PATIENTS

The information presented thus far has demonstrated a common theme amongst the literature supporting the beneficial effects of exercise during the cancer continuum. These effects include biological, psychological, and financial. Variables within study design such as exercise type, cancer type and time of intervention within the cancer continuum all influence the degree and significance of the results. Clinical reasoning in healthcare is based upon the evaluation of both beneficial effects against the risk of adverse effects of any proposed treatment regime. Thus, it would seem pertinent to report adverse effects to exercise treatment within the cancer continuum (Figure 1, Table 2).

A recent systematic review and meta-analysis in exercise oncology focused on the biological and psychological effects, safety and feasibility of exercise in breast cancer patients with stage II or greater disease (Singh et al. 2018).The authors noted there was a lack of data surrounding adverse events attributed to exercise. In fact, only 15 of the 61 studies reported information on adverse events, with a total of 116 adverse events reported. A plausible reason for this is representative of the inherent fault in such trials that patients who suffered an adverse event would potentially go unacknowledged or unreported because they would withdraw from the trial without explanation or reason. In the systematic review and meta-analysis, it was stated that of the 15 trials that did report on adverse events, 58% were considered unrelated to exercise and 42% were exercise related (Singh et al., 2018). Further investigation revealed exercise related adverse events that occurred were between grade 1-3. Grade 3 is

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defined as 'severe or medically significant but not immediately life-threatening, hospitalization and/or prolongation of hospitalization indicated, disabling and limiting self-care activities of daily living' (National Cancer Institute 2009). There was a total of six grade 3 events for the following causes: headache, physical accident, severe discomfort, dizziness, and foot pain requiring surgery. In an earlier systematic review and meta-analysis of 82 studies on exercise interventions in cancer (mixed types) survivors, only 36 reported the presence or absence of adverse events (Speck et al. 2010). One of the trials that was reviewed was a randomized controlled trial of 641 long-term mixed cancer-type survivors prescribed a home-based exercise program (Morey et al. 2009). One of the inclusion criteria was that participants were older and overweight. Among the data, there were 201 adverse events reported, of which only five could be directly attributed to the exercise intervention. These events were reported as: increased blood pressure, hip pain, strained hamstring, falls and calf pain. They noted that there was no difference in the incidence of these events between the exercise or control group. A randomized controlled trial investigating the safety and efficacy of weight training in 85 breast cancer survivor patients reported that over the duration of the trial (12 months) there was a total of 13 reported adverse events attributed to the exercise intervention (Schmitz et al. 2005). The injuries reported included back (n=6), ankle (n=3), wrist (n=1), leg pain (n=1), heel spurs (n=1) and rotator cuff (n=1). It was reported that these injuries did not persist longer than a few weeks and there were no long-term consequences or impact on activities of daily living. In addition, some trials reported more concerns about the incidence of adverse events which were more likely to occur in the cohort of cancer patients that were undergoing active treatment specifically with respect to anemia, lymphedema and weight loss (Speck et al. 2010). Contrary to these concerns, studies have investigated the intervention of exercise on hemoglobin levels, generally finding a lack of association with anemia. In fact, fatigue and physical performance levels in a 6 week intervention of a vigorous aerobic exercise program were noted in patients who had just completed a high dose of chemotherapy and autologous peripheral stem cell transplantation (Dimeo et al. 1998). This was a pilot study with only 16 cancer participants in each of the control and training

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groups. The results showed a significant improvement in hemoglobin concentration (between baseline and immediately upon completion of the training program 7 weeks later) in the training group compared to the control group. Likewise, in an earlier study, hemoglobin levels improved in anemic cancer patients actively receiving treatment (darbepoetin alfa) following participation in an aerobic exercise regime (Courneya, Jones, et al. 2008b). The pharmacological action of darbepoetin alfa is to increase hemoglobin levels, the authors concluding that patients who are receiving this drug require monitoring to ensure their hemoglobin levels do not exceed therapeutic levels.

Another long-standing controversy around exercise in cancer patients, centers around the idea that strenuous upper body exercise can cause exacerbation or development of lymphedema in breast cancer patients that have had surgical resection. A 1996 study first challenged this assertion by assigning female cancer patients, who had received axillary dissection with lymph nodes removed, a vigorous upper body exercise program (aerobic, stretching and resistance exercises) for a 7-8-month period. Various arm circumference measurements (elbow, wrist, and hand) were recorded at three intervals (baseline, 2 months, and 7-8 months). The study recruited 20 women aged between 31-62 years with a time since cancer diagnosis of between 1-17 years. Results showed no clinically significant increases in circumference of the affected limb nor any other adverse events reported. Other similar (and larger) studies more recently have reported similar conclusions of no significant risk to patients in developing or worsening lymphedema symptoms with strenuous upper body exercise, however they have also shown no significant improvements in lymphedema progression (Cheema et al. 2008). They postulated that the benefits in breast cancer patients participating in a strenuous exercise program are related to the general biological and psychological benefits of activity.

The data available on the adverse effects of exercise in cancer patients is limited in the current literature largely due to flaws in design. This can serve to inform future trials to include data relating to safety and patient withdrawal as subtopics. However, there is a general consensus amongst researchers that the risk of adverse effects of exercise in the cancer continuum is low. However, it is strongly

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recommended that all exercise is prescribed by educated health professionals and tailored to the patient with all aspects of their cancer considered i.e., type, time in the continuum, pre-existing co-morbidities, psychological factors.

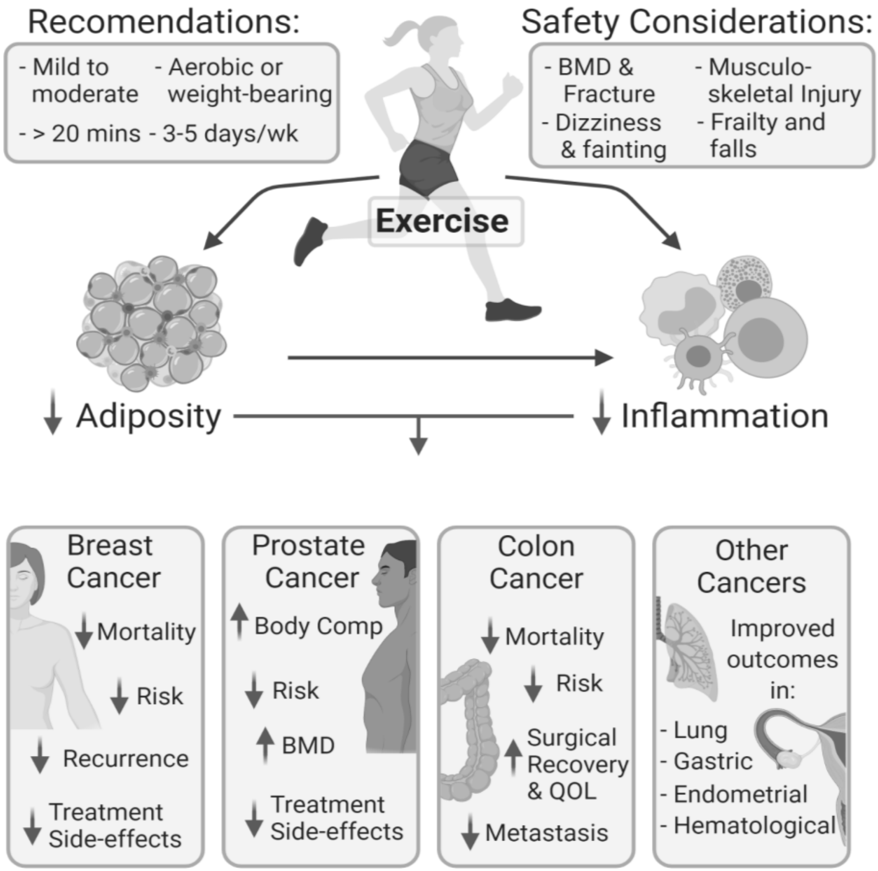

Figure 1. The beneficial effects of exercise and cancer and some safety considerations.

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Table 2. Exercise and adverse events in cancer patients

Study (Ref)	**Physical activity**	**Cancer Continuum**	**Participants**	**Biological mechanism/ Health**	**Positive surrogate or clinical outcomes**	**Adverse event reported**
Breast Cancer						
RCT (Schmitz et al. 2005)	One year (intervention) vs delayed 6month (control) resistance training upper and lower body	Post breast cancer treatment	Average age: 53.3 years, intervention group, 52.8 years control group, breast cancer survivors	Body composition, insulin	Continued 12month group; - Increase in lean mass - Decrease in body fat and IGF-II	- 13 injuries all MSK; 1 requiring surgery
Series of case reports (Harris and Neisen-Vertommen 2000)	7-8 months combined supervised and home based aerobic, strength and stretching upper body program	Post breast cancer surgery treatment	31-63 year old female breast cancer post axillary dissection surgery	Arm circumference (indicative of lymphedema presence)	- No increase in arm circumference	- No adverse events reported
Mixed Cancer						

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Table 2. (Continued)

Study (Ref)	Physical activity	Cancer Continuum	Participants	Biological mechanism/ Health	Positive surrogate or clinical outcomes	Adverse event reported
RCT (Morey et al. 2009)	One year home based tailored MVPA + TC + motivational and self monitor workbook + diet advice + pedometer	Long-term mixed cancer post treatment	65 – 91 year old, BMI 25+, men and women long-term mixed cancer survivors	Self-reported physical function scale, dietary behaviour, BMI and QoL	- Improved physical function - Improved dietary behavior - Decreased BMI - Improved QoL	-2 01 adverse events - 5 attributed to exercise intervention - Events consisted of 3 MSK strains, 1 increase in blood pressure and 1 a fall
RCT (Courneya et al. 2008)	12 week supervised aerobic exercise program	During mixed cancer treatment	25-77 year old, male and female non-myeloid cancer with Hb 80-110 g/L and receiving darbepoetin alfa	QoL, fatigue, Hb levels, respiratory fitness (VO2peak), darbepoetin alfa dosing.	- Improved QoL and fatigue levels - Improved Hb levels and thus reduced darbepoetin alfa dosing levels required - Improved VO_2 peak levels	- No reported adverse reaction however suggestion to monitor Hb levels in case exceed therapeutic dose

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Study (Ref)	**Physical activity**	**Cancer Continuum**	**Participants**	**Biological mechanism/ Health**	**Positive surrogate or clinical outcomes**	**Adverse event reported**
Pilot Study (Dimeo et al. 1997)	6 week supervised aerobic exercise	Immediately post high dose chemotherapy treatment	Training group 42 years old + 9 control group 39 year old + 11 male and female	Physical performance, Hb concentration	- Improvements in physical performance - Increase in Hb concentration	- No reported adverse reaction

Abbreviations: TC, Telephone Counselling; MVPA, Moderate Vigorous Physical Activity; QoL, Quality of Life; Hb, Hemoglobin; MSK, Musculoskeletal.

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Conclusion and Future Prospects

Whilst much of the literature pertaining to the impact of exercise in cancer patients and survivors can be varied, there is much consensus that these cohorts are particularly vulnerable to physical inactivity as a result of treatment and/or diagnosis. Exercise of moderate to vigorous intensity and volume is shown to be safe and can reduce the incidence of risk factors associated with multiple cancers. It is also shown to reduce the mortality rate of cancer survivors. Well-known biological mechanisms have been identified which can explain how physical activity inhibits cancer cell growth through immune function, systematic low-grade inflammation, adiposity related biomarkers and reproductive hormones (Apostolopoulos et al. 2014; Pudkasam et al. 2017). It is evident that some biomarkers change after exercise training in people with cancer. Nevertheless, more understanding around the biomarkers and biological pathways that occur in response to exercise training is essential to gaining insight into its effects on cancer.

Approximately one third of research studies about exercise oncology reported that exercise may have adverse effects in people living with cancer. However, there were no reports of serious adverse effects or life-threatening events. The most common side-effects after exercise consisted of muscle injuries, pain, tension headaches and dizziness. The symptoms are likely to happen in people with cancers who are older and obese. Importantly, exercise should be cautioned for people living with cancer who have severe hematological disorders following chemotherapy or radiotherapy.

Most physical activity and exercise studies in people living with cancers have been conducted in the most common cancer types such as breast, colorectal and prostate cancer. However, there is a need for further research into less common cancer types such as endometrial, gastrointestinal, lung and hematological cancers, as the components of effective and safe exercise programs may be different depending on the type and stage of cancer, and the treatments they receive. All cancers are individual in their nature, pathophysiology and management hence, the specific health outcomes from an exercise intervention can vary greatly. Outcomes from exercise interventions in one patient population cannot be inferred to others, as such, further

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research is required into other less common cancers focusing on safety, volume of exercise training and the biological mechanisms underlying any improvements in their physical and psychological health.

Physical activity is recognized as having beneficial effects to the psychological health to the general population (Mikkelsen et al. 2017), improvements to menopausal symptoms in women (Stojanovska et al. 2014) and improvements to quality of life to those living with breast cancer (Pudkasam et al. 2018). One challenge however, is for cancer patients to stay motivated in a physical activity program. Many psychological theories have been applied to promote physical activity adherence (Pudkasam et al. 2018). In fact, we are conducting a study (PAPHIO study) to determine the psychological concepts related to behavioral change consisting of self-monitoring by a step tracker with or without motivational interviewing (Pudkasam et al. 2020). In the PAPHIO study breast cancer survivors are encouraged to undertake self-directed physical activity in a 2x2 crossover design study for 24 weeks with quality of life, psychological health and immune changes being assessed (Pudkasam et al. 2020). Supervised exercise can be considered as a safe and effective adjunct therapy in the management of patients with a wide range of malignancies. It is able to improve both cancer outcomes and side effects of the primary treatments. Even in cancer types that have not been thoroughly researched, given the low risk profile, and general health promoting effects, exercise is likely to be a beneficial intervention in all patients.

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Chapter 12

ROLE OF EXERCISE TRAINING IN PREVENTING CARDIAC DYSFUNCTION IN BREAST CANCER SURVIVORS

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ABSTRACT

Breast cancer is the most incident malignant-tumor and ranks as the leading cause of cancer-related death among women worldwide. Over the last decades, remarkable advances in the management of breast cancer (diagnostic and therapeutic innovation) have been achieved, improving clinical outcomes and cancer-specific survival. However, patients living with and beyond breast cancer may face several short and long-term treatment-related side effects.

Cardiotoxicity is a major issue in clinical practice, that may restrict or delay treatment options. In fact, cardiovascular disease has been suggested as a common cause of death in breast cancer

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survivors and therefore, preventive strategies are needed. Exercise training is well recognized as a safe and effective approach to prevent or mitigate some treatment and cancer-related side effects. This chapter will address the role of exercise in preventing cardiac dysfunction associated with chemotherapy in breast cancer.

Keywords: exercise training, breast cancer, chemotherapy, cardiac function

INTRODUCTION

With more than 2 million new cases diagnosed worldwide in 2018, breast cancer is the most diagnosed malignant disease and one of the main causes of cancer-related deaths in females (Bray et al., 2018). Over the last few decades, the breast cancer incidence rate has increased slightly by 0.3% per year and is expected to continue to rise over the coming decades (American Cancer Society, 2020). In contrast, due to progress in cancer management including primary prevention, screening, and curative-intent therapies, breast cancer mortality has been decreasing, which has led to an improvement in the number of cancer survivors. In the United States, there are over 3.8 million breast cancer survivors. This number is justified by high 5-year and 10-year disease-specific survival rate of women with breast cancer, which is now of 91% and 80%, respectively (American Cancer Society, 2020).

Despite the longer survival, breast cancer survivors often faced multiple different short and long-term side effects from cancer and related treatments (American Cancer Society, 2020; Bodai & Tuso, 2015). In particular, cardiovascular toxicity, a term which refers to the adverse events on the cardiovascular system, is recognized as a major concern in clinical practice, given that it may be associated with restriction or discontinuation of cancer treatments (Chuy & Yu, 2019). In fact, cardiovascular disease has been identified as one of the main causes of morbidity and mortality among breast cancer survivors, especially in patients with advanced age (Bradshaw et al., 2016; Abdel-Qadir et al., 2017). In the setting of breast cancer management, it is

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well recognized that the usual exposure to a number of therapeutic modalities including: traditional therapies (i.e., conventional chemotherapeutics such as anthracyclines or mediastinal radiotherapy) or to the anti-HER2 newer molecular targeted therapies (such as trastuzumab) is associated with the risk of developing cardiovascular toxicity, which is usually manifested by, but not limited to, left ventricular dysfunction which precedes overt heart failure (Chuy & Yu, 2019; Zamorano et al., 2016). In addition to the direct effects of cancer treatments, indirect consequences (e.g., sedentary lifestyle, physical deconditioning, weight gain) should also be considered for the assessment of cardiovascular risk. The implementation of cardioprotective strategies is warranted. The use of dexrazoxane or other drugs commonly used in the management of heart failure (such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blocker, beta-blockers and statins) has been recommended by scientific societies (Zamorano et al., 2020). However, literature shows that the direct and indirect adverse effects of cancer treatments extend beyond the heart affecting the entire cardiovascular system including the pulmonary-vascular and blood-skeletal muscle axes. A striking example is the marked impairment in cardiorespiratory fitness, which is a well-recognized outcome of global cardiovascular function. Besides inversely correlating with both cardiovascular-related, cancer-related, and all-cause mortality, poor levels of cardiorespiratory fitness (measured by peak oxygen consumption), is associated with higher fatigue levels, exercise intolerance and lower health-related quality of life. Data obtained after different treatment regimens revealed that the cardiorespiratory fitness of these patients may decrease by up to 26% and may not recover to the baseline values. In a non-randomized trial, Howden et al., (2019) observed a 15% reduction in peak oxygen consumption in women with early-stage breast cancer (n = 14) after an anthracycline-containing chemotherapy (AC) (before AC: 1.62 ± 0.43 L/min vs. after AC: 1.38 ± 0.47 L/min). This decrease is clinically relevant because it demonstrates that in a relatively short period of chemotherapy (4 months) is sufficient to lead to change that would normally be expected with 15 years of aging. In contrast, the authors verified that a group of patients (n = 14) who were engaged in a program of aerobic training and resistance exercises during AC, with

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two supervised exercise sessions during 8 to 12 weeks, were able to mitigate the decline of cardiorespiratory fitness (before AC: 1.79 ± 0.34 L/min vs. after AC: 1.69 ± 0.29 L/min). A recent meta-analysis, which includes 48 randomized controlled trials (representing 3,632 patients) demonstrated that exercise training was associated with a significant increase in cardiorespiratory fitness (+2.80 mL.kg.min-1) compared with no change in the usual care group (Scott et al., 2018). These findings support the inclusion of exercise as a effective therapeutic modality to mitigate the deconditioning of the cardiorespiratory system among cancer survivors.

Preclinical data have demonstrated the potential role of exercise training to protect cardiac function by increasing antioxidant activity and, so, preventing reactive oxygen species release and increase in heat shock proteins; decrease proapoptotic signal; and attenuate markers of cardiomyocyte mitochondrial dysfunction (Kirkham & Davis 2015). So far, few studies have explored the impact of exercise on cardiac outcomes beyond cardiorespiratory fitness and so this potential cardioprotective effect remains unknown. In a single-arm trial with 17 women with breast cancer receiving adjuvant trastuzumab, Haykowsky et al., (2009) were the first authors exploring the effects of an exercise program in preventing left ventricular remodeling. The intervention consisted of a 3 weekly supervised aerobic training performed, during 30 min to 60 min at a heart rate equivalent to 60% to 90% of peak oxygen consumption, over the first 4 months of adjuvant trastuzmab. Although the authors hypothesized the protective effect of exercise, this approach did not prevent the left ventricular remodeling. On the other hand, in a randomized controlled trial, involving 47 women with breast cancer during adjuvant trastuzumab, Hojan et al., (2020) showed that an exercise intervention, with 5 sessions per week for 9 weeks, combining aerobic training and resistance training was able to significantly alleviate the decline in left ventricular ejection fraction in the exercise group compared to control. These distinct results are likely to be explained by differences in sample size, exercise intervention design, and, perhaps above all, due to the fact that Hojan et al., (2020) reported a greater adherence to the intervention. Moreover, three small randomized controlled trials, with different exercise approaches, analysed the effects of exercise anthracycline-related cardiotoxicity

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(Hornsby et al., 2019; Kirkham et al., 2018a; Ma, 2018). Kirkham et al., (2018) explored the effect of a "short dose" exercise intervention involving a single 30 min bout of aerobic exercise, at a vigorous intensity, performed 24 hours prior to each AC cycle (i.e., maximum of 4 exercise sessions). The authors observed that exercise significantly attenuated N-terminal pro b-type natriuretic peptide (NT- proBNP) but no significant effects were observed in cardiac function outcomes. The same results were obtained by Hornsby et al., (2014) after delivering a nonlinear aerobic training exercise program with duration ranging from 15-20 minutes to 30-45 minutes and intensity ranging from 60% to 100% of power output. On the other hand, Ma (2018) adopted a linear exercise intervention with 3 sessions per week for 12 weeks, involving 50 minutes at intermittent intensity ranging 50% to 95% of maximum heart rate. The authors showed a significant attenuation in left ventricular ejection fraction decline in the exercise group compared to control. Despite this suggests that exercise training may potentially prevents cardiac dysfunction, more studies are warranted to analyse this hypothesis and to identify the optimal FITT (frequency, intensity, time, type) prescription to target this outcome.

Considering the well-established role of exercise training in cardiac rehabilitation, the American Cancer Society and the American Heart Association have introduced the concept of cardio-oncology rehabilitation (Gilchrist et al., 2019). In fact, literature regarding the cardiac rehabilitation field, shows that continuous aerobic exercise, at moderate intensity, has been associated with improved left ventricular ejection fraction in heart failure patients, but that benefit was not evident when resistance training was performed alone or combined with aerobic training (Chen et al., 2012; Jewiss, Ostman & Smart, 2016; Tucker et al., 2019). Furthermore, Tucker et al., (2019) highlight that the efficacy of moderate intensity continuous aerobic exercise on LVEF and VO2peak are greatest in long-term interventions (length ≥ 6 months). Such results emphasize the importance of implementing interventions that last longer than the AC-T regime, which range from 8 (dose-dense protocol) to 12 weeks (every three weeks protocol).

Observational studies also highlight the beneficial impact of exercise on cardiovascular health. In a study involving a cohort of 2,973 women diagnosed with early-stage breast cancer (median age of

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57 years, 8.6 years median follow-up), Lee and colleagues (2016) analysed the impact of post-adjuvant therapy exercise exposure on both cardiovascular-related and all-cause mortality. The authors verified that adherence to exercise guidelines for adult cancer survivors (i.e., >9 MET-hour/week) was associated with a clear reduction (23%) in the incidence of cardiovascular events, when comparing with patients not meeting these guidelines (Jones et al., 2016). Moreover, the authors also found a strong dose-response relationship suggesting that engaging in more exercise beyond this minimal recommendation may provide greater cardiovascular protection. Similar results were reported by Okwuosa et al., (2019), verifying a beneficial effect of pre-diagnosis breast cancer exercise in reducing the risk of cardiovascular events in a cohort of 4,015 patients. Exercise during cancer survivorship should be considered as a promise and low-cost intervention to reduce the risk for cardiovascular disease risk in women breast cancer survivors.

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Katherine Harkin is bachelor of Science, Master of Health Science, GCINP, Graduate Certificate in Tertiary Education, Master of Science by Research (candidate) Katherine Harkin has been a practicing Australian osteopath since 1999 with extensive and varied clinical experience in Australia, Europe, United Kingdom, Ireland and India. She has undertaken further qualifications and training in advanced musculoskeletal rehabilitation in sporting, post-surgical, pregnancy, paediatric and geriatric cohorts as well as in tertiary education. Katherine has also been involved in curriculum development and academic education of undergraduate and postgraduate allied health professionals in prominent Australian and International Universities since 2001. In addition to her private clinical practice, Katherine is currently employed by Victoria University where she is key academic, unit convenor and lecturer of various anatomy, physiology, clinical skills and communication subjects to first year allied health students. Currently, she is pursuing her interest in research as the primary investigator in a clinical trial on the impact of physical activity on various health outcomes in female breast cancer survivors.

Kathy Tangalakis, Bachelor of Science (Honours), PhD A/Prof Kathy Tangalakis, BSc (Hons), PhD *(UniMelb)*, is a senior academic at Victoria University (VU). Her PhD investigated the impact of maternal stress on fetal development. Her career focus has been on enhancing the student learning experience and outcomes for diverse commencing student cohorts in Biomedical and health-related courses. Kathy's contribution to learning and teaching has been recognised with 8 Vice-Chancellor's awards and nationally in 2016, with an Australian Award

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for University Teaching and the Michael Roberts Medal for Excellence in Physiology Education from the Australian Physiological Society. In 2019 she was awarded the David Jordan award from the UK Physiological Society. Kathy is currently Head of Scholarship & Professional Learning and chair of the award-winning Women in First Year (WiFY) network at VU. She is also co-chair of the National Biomedical Assessment Collaboration, comprising 25 Australian universities, whose aim is to build a national Assessment Framework which will drive improvements to the quality of assessments in the Biomedical and BioSciences. She is currently part of a study investigating the benefits of exercise in breast cancer survivors.

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problems and their solutions. He is an Honorary Fellow of the Faculty of Occupational Medicine, an expert adviser to the UK government Work and Health Unit, and a member of the Industrial Injuries Advisory Council. Kim's current research focuses on exploring the nature of obstacles to participation for people with common health problems, including developing novel rehabilitation and educational interventions. His current passion is using knowledge mobilisation to inform policy and practice that can maintain participation for people with health problems.

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Maria Rosa Bernal Lopez is PhD in Biochemistry and Molecular Biology from the Autonomous University of Madrid. Currently, she is the Research Coordinator of the Department of Internal Medicine in the Regional University Hospital of Malaga, as well as Co-Investigator Responsible for Diabetes, Obesity and other Vascular Risk Factors: Systemic Autoimmune Diseases Group (A-06) at the Instituto de Investigación Biomédica de Malaga (IBIMA) and Head of the Research Group of the Andalusian Plan for Research, Development and Innovation (PAIDI), Pathology of Atherosclerosis, Diabetes and Obesity (PADO CTS-1023). In addition, she is a Collaborating Researcher attached to the Ciber Fisiopatología de la Obesidad y la Nutrición (CiberObn CB06/003) belonging to the Carlos III Health Institute. The latest projects in which MRBL is principal investigator are related to lifestyle modification to prevent cardiovascular diseases. She is an expert in clinical and basic obesity research, focusing on the active metabolism of obese diabetic patients and metabolically healthy obese patients. She has different fields of study among which are diabetes, inflammatory processes and cardiovascular risk factors, as well as the molecular and cellular analysis of various diseases.

Marie-Carmen Neipp is a PhD in Psychology from the Miguel Hernández University of Elche UMH. Since 2002, she is a lecturer of Psychology in the Department of Health Psychology at UMH, she is a deputy vice-chancellor for studies of UMH since 2015. Moreover, she is an Advanced Solution-Focused Practitioner. Her major research interests lie in the area of Health Psychology. She has a general interest in the subject as a whole but have special interest in studying different psychosocial variables (control beliefs, coping, quality of life, physical exercise, etc) and their influence on people well-being.

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Furthermore, since 2017 my research interest also lies in studying how different variables related to positive psychology (resilience, optimism, emotional intelligence, positive emotions, etc) are related with well-being. She has published numerous research papers in the area of health psychology. She has participated as a lecturer in different national and international events and conferences.

Matthew Haines is Head of Division of Sport, Exercise & Nutrition Sciences at the University of Huddersfield. He is a Chartered Scientist and a BASES Accredited Sport and Exercise Scientist (Physiology), and a BASES Certified Exercise Practitioner (Obesity and Diabetes Specialist). His area of expertise is sport and exercise physiology including the effects of high-intensity interval training on perceptual and physiological outcomes. He has developed research interests including exercise and physical activity and the effects on women with polycystic ovary syndrome (PCOS), obesity, and type 2 diabetes. He also has a special interest in pragmatic research to translate the benefits of exercise and physical activity into real world settings. Prior to working in academia, Matthew has extensive experience of working in the fitness industry including exercise referral and personal training for people with a wide range of chronic health conditions including obesity, type 2 diabetes, cardiovascular disease, and cancer.

Pedro Antunes, Degree of Sport Science, Master of Sport Science (Exercise and Health), is an exercise physiologist with specific training and experience in supervising exercise training programs for cancer patients, particularly for women with breast cancer, after or during treatment. Pedro Antunes received a doctoral research scholarship from Fundação para a Ciência e Tecnologia and is conducting his PhD at University of Beira Interior (Portugal). The main aim of his PhD research is to investigate the role of exercise training in cardiac function of women with early breast cancer receiving anthracycline-containing chemotherapy.

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Priscila C. Nascimento, DDS, MSc, is a PhD student at the Federal University of Pará (UFPA). She has experience in Dentistry, with emphasis on toxicological effects of heavy metals and ethanol in the oral cavity tissues as well as central nervous system. She also develops systematic reviews and meta-analyses of studies on issues related to biomedical sciences. She is a member of the Structural and Functional Biology Laboratory, at the Biological Sciences Institute at UFPA.

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Railson O. Ferreira, DDS, PT, MSc is a PhD student at the Federal University of Pará (UFPA), and professor of periodontology at University Center FIBRA, BELÉM, PA, BRAZIL. He has experience in Dentistry, with emphasis on toxicology effects of ethanol in the oral cavity tissues, periodontology; and also investigates the systemic effects of exercise in oral and general health. He also develops systematic reviews and meta-analyses studies related to exercise and oral health. He is a member of the Structural and Functional Biology Laboratory, at the Biological Sciences Institute at UFPA, whose leader is Prof. PhD Rafael Rodrigues Lima.

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Ricardo Gomez Huelgas. Professor at the Faculty of Medicine (Department of Medicine and Dermatology) in the University of Malaga (Andalusia, Spain). He is director of the Department of Internal Medicine of the Regional University Hospital of Malaga and. He is an expert in Epidemiology and Clinical Research at the Andalusian School of Public Health and in recent years has published numerous papers on topics related to obesity and metabolism in high-impact journals. He is the researcher responsible for the consolidated group of Diabetes, Obesity and other Vascular Risk Factors: Systemic Autoimmune Diseases (IBIMA A-06) of the Instituto de Investigación Biomédica de Malaga (IBIMA); and head of the Research Group of the University of Malaga: Epidemiology and Molecular Mechanisms of Human Inflammatory, Autoimmune and Vascular Pathologies (EPIMIAV. CTS-656). Moreover, he is a Collaborating Researcher in the Ciber Fisiopatología de la Obesidad y la Nutrición (CiberObn CB06/003) belonging to the Carlos III Health Institute. Dr. Gómez Huelgas has sufficient antecedents in the field of developing the study framed in the analysis of the lifestyle modifications. All his directed projects gave rise to national and international publications.

Robert Naughton, PhD, is a Senior Lecturer in Sport, Exercise, and Nutrition Sciences at the University of Huddersfield. He is an accredited nutritionist with the Sport and Exercise Nutrition register (SENr). Robert's research background is predominantly within exercise physiology and nutrition, ranging from methods to improve athletic performance to promoting healthy ageing through targeted nutrition and exercise strategies.

Sharon Newson is an exercise practitioner with vast experience assisting people living with chronic health conditions including obesity, diabetes, cancer, cardiovascular disease, depression, anxiety, mobility issues, and back pain. She is a pracademic combining personal experience, professional knowledge, and a big-picture approach offering client-centred approaches to help people with their physical, spiritual, and psychological health and wellbeing. Sharon has worked

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privately and in gym-based environments, as well as holding a Lead Instructor position on a community-based exercise referral scheme in South Yorkshire. She has worked in a voluntary capacity with Verity UK (English PCOS charity) as a Local Group Leader for seven years, contributed to booklets on PCOS for healthcare professionals, and spoken at their annual conference. Sharon is a doctoral researcher at University of Huddersfield investigating polycystic ovary syndrome (PCOS), exercise, and eudaimonic wellbeing. Her research programme explores how self-acceptance, positive relations with others, personal growth, purpose in life, autonomy, and environmental mastery are impacted by PCOS, and how this may further effect exercise and health behaviours. She has designed a novel physical intervention which combines small group self-help discussion with regular exercise for women living with PCOS.

Supa Pudkasam is bachelor of Nursing Science (Nursing and Midwifery), Master of Science (Exercise Physiology) Supa Pudkasam has been a nursing instructor of Nursing Science Faculty, Assumption University, Thailand since 2004. She has experience in teaching and supervising of nursing students in adult nursing practicum. She has just submitted her PhD thesis at Victoria University, Melbourne, Australia. She had received a scholarship from Assumption University, Thailand to study PhD at Victoria University between 2016 and 2020. She was appointed as an Honorary researcher of Western Health between 21 November 2019 and 31 December 2020 to conduct a clinical trial "Physical activity adherence, psychological health and immunological outcomes (PAPHIO study) in breast cancer survivors" which was part of her PhD research. Her research interests involve physical activity or exercise for health promotion in people with chronic diseases.

Vasso Apostolopoulos is bachelor of Science (Honours), Advanced certificate in Protein Crystallography, PhD Professor Vasso Apostolopoulos received her PhD in 1995 from the University of Melbourne and Advanced certificate in Protein Crystallography University of London. Her expertise is in the areas of immunology,

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crystallography, cellular biology, translational research and development of drugs and vaccines. Vasso has lead/Directed a number of research programs at the Austin Research Institute, the Burnet Institute, Centre for Chronic Disease at Victoria University, and, at the Institute for Health and Sport, VU. She was the Deputy Vice-Chancellor Research (interim), the Pro Vice Chancellor Research Partnerships and is currently the Associate Provost (Research Partnerships) at Victoria University. Vasso has received >100 awards, published >405 research papers and books, is an inventor on 18 patents and 90 sub-patents and her current interests are treating chronic diseases with an immunological focus, in particular in the areas of cancer, autoimmune disorders and mental health. More recently, her lab is working on exercise immunology and how to treat disease using exercise. Is exercise the new immunotherapy?

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