EXERCISE, BODY COMPOSITION, CARDIORESPIRATORY FITNESS AND MENOPAUSAL CHARACTERISTICS: EFFECTS AND INTERACTIONS

Doctoral Thesis in Sport Sciences

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Exercise, body composition, cardiorespiratory fitness and menopausal characteristics: effects and interactions

This academic dissertation was submitted with the purpose of obtaining a doctoral degree in Sport Sciences according to the provisions of Portuguese Decree-Law 115/2013 of August 7th. This thesis was supervised by Maria Helena Rodrigues Moreira, PhD, of the University of Trás-os-Montes and Alto Douro and co-supervised by Catarina Isabel Neto Gavião Abrantes, PhD, and Ronaldo Eugénio Calçada Dias Gabriel, PhD, also from the University of Trás-os-Montes and Alto Douro.

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“Whenever I encountered a grown-up who seemed to me at all enlightened, I would experiment on him with my drawing Number One, which I have always kept. I wanted to see if he really understood anything. But he would always answer, “That’s a hat.” Then I wouldn’t talk about boa constrictors or jungles or stars. I would put myself on his level and talk about bridge and golf and politics and neckties. And my grown-up was glad to know such a reasonable person.”

Antoine de Saint-Exupéry in *The little prince*

“Dear Teacher,

I’m a survivor of a concentration camp. My eyes saw what no man should witness: gas chambers built by learned engineers, children poisoned by educated physicians and infants killed by trained nurses. Women and babies shot and burnt by high school and college graduates. So I’m suspicious of education.

My request is: help your students become human. Your efforts must never produce learned monsters, skilled psychopaths, educated Eichmanns. Reading, writing, arithmetic are important, but only if they serve to make our children more human. …”

*Dr. Haim Ginott in “Teacher and Child” (Excerpt of a letter written by a Holocaust survivor to educators)*
This Thesis is dedicated to

the ones with honor and unconquerable soul,
that have not winced nor cried aloud;
Those whose head is bloody, but unbowed.
The rule breakers and the revolutionaries.

Because sometimes, the hand that feeds you, needs a good bite.

Je suis Charlie!
These last four years have undoubtedly been some of the most challenging of my life, being plentiful of difficulties and uncertainties, which tested my resiliency sometimes close to limits. Only in academia are you in this bizarre world that never ends; where you always could, or should, do more. Meanwhile, the project we thought it was cool is, actually impossible, or someone’s has already done it... and, in any event, nobody actually cares. -- As a result, there’s a constant anxiety that stops PhD students from doing what they enjoy doing. Instead, we feel like impostors, and that the rest of the world is moving light years ahead with their social lives. All of this can lead to burn out. -- Nevertheless, I was lucky enough to be surrounded by a number of people that helped me to overcome each of the difficulties that successively stood on the way.

Por estes motivos, este é o único capítulo da Tese escrito (ainda que não na totalidade) em português, pois destina-se a partilhar o meu reconhecimento e gratidão por todos aqueles que contribuíram (pessoas e instituições) para que este trabalho pudesse ser desenvolvido e, finalmente, concluído. -- É também, o único espaço em que o discurso não acontece no plural, mas na primeira pessoa do singular. Não se trata de vaidade, pelo contrário. Só o discurso e a responsabilidade no singular me permitiriam justamente reconhecer e revelar o nome de todos, e cada um, daqueles que estão encobertos por detrás do we (nós) nos restantes capítulos. E por isso, talvez sejam estas as linhas mais difíceis de escrever.

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...

At the end, thanks to you, reader. If you are reading this line after the others, you at least read one page of my thesis. Thank You.

Sincerely,

Florbela da Rocha Aragão
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List of Publications and Presentations

During the developmental stages of this thesis, some work has been published, accepted or submitted for publication in peer-reviewed journals, as well as presented at scientific meetings originating some publications in proceedings and abstract books. Next we present a selection of the publications and communications specifically related with the work developed in this thesis.

Book chapters


Peer-reviewed papers in international journals (ISI)


Abstracts in conference proceedings with scientific refereeing (JCR)


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List of Abbreviations

ACSM  American College Of Sports Medicine
BMR  Basal Metabolic Rate
CRF  Cardiorespiratory Fitness
EE  Energy Expenditure
EVFNSA  Elevated Visceral Fat Area and Non-Sarcopenic
EVFSA  Elevated Visceral Fat Area and Sarcopenic
FCT  Portuguese Foundation For Science and Technology
FFM  Fat-Free Mass
FM  Fat Mass
HR  Heart Rate
HRmax  Maximal Heart Rate
HRR  Heart Rate Reserve
HT  Hormone Therapy
NONSA  Non-Obese and Non-Sarcopenic
NVFNSA  Normal Visceral Fat Area and Non-Sarcopenic
ONSA  Obese and Non-Sarcopenic
OSA  Obese and Sarcopenic
PM  Postmenopausal Women
RER  Respiratory Exchange Ratio
rpm  Revolutions per Minute
SM  Skeletal Muscle Mass
TM  Time Elapsed Since Menopause
VFA  Visceral Fat Area
VO2max  Maximum Oxygen Uptake
VT’s  Ventilatory Thresholds
W  Weight
Abstract

Today, most women live long enough to become menopausal and approximately one-third of women’s lives will be lived in postmenopause. As the number of postmenopausal women in our society increases, so does the significance of the prevention of frailty, active aging, and quality of life. Thus, due to the great social importance and impact worldwide, women’s health and menopause became a rapidly expanding field in need of scientific investigation. Therefore, evaluating the research on interventions or programs that target health promotion during this physiologically complex stage is essential to help and guide into more effective interventions.

Consequently, the main aim of this thesis was to analyze the interaction of the menopausal characteristics with exercise and physical fitness, to evaluate optimal cardiovascular exercise intensities, and to examine the effects of this 12-month multicomponent exercise program on body composition. Therefore, knowledge of such interactions would help physicians and sport-science and fitness professionals move toward appropriate exercise prescription. To refer that, this thesis is included in the “Shape Up During Menopause” study – a randomized, controlled trial approved by the Portuguese Foundation for Science and Technology – that aims to improve overall health-related components of physical fitness and fall risk of PM through a 12-month moderate-to-vigorous exercise program (combining step aerobics, muscle strength, and flexibility/postural control training).

Our overall results suggest an impairment of cardiorespiratory fitness with increasing age and time elapsed since menopause, but especially in the presence of increased total and central adiposity or reduced SM index. However, the 12-month moderate-to-vigorous exercise program seems to, positively and meaningfully, influence all the anthropometric and body composition variables along with the basal metabolic rate. In addition, no interactive effects were found between the exercise and menopausal characteristics, suggesting that exercise alone can promote improvements in postmenopausal women’s body composition. Furthermore, our results exposed that the upper limit of 84% (proposed by de ACSM) overestimates the %HRR value at the second ventilatory threshold, and the 40% of HRR lower limit is strongly related to the first ventilatory threshold, suggesting that, the cardiorespiratory target zone for this population should be lower (40%-70%HRR) than that recommended for the general population. Our results also demonstrate that, regarding postmenopausal women’s body composition, it seems to be unnecessary to make specific adjustments in the exercise prescription due to the individual menopausal characteristics – suggesting that, exercise programs with similar doses (as those of described in “Shape Up During Menopause” program) should be offered to women interested in this type of program.

Keywords: Cardiorespiratory fitness, Body composition, Characteristics of menopause, Postmenopausal women, Exercise Program, Guidelines, Ventilatory thresholds
Resumo

Hoje, a maioria das mulheres vive tempo suficiente para atingir a menopausa, na verdade, aproximadamente um terço da vida das mulheres será vivido na pós-menopausa. À medida que aumenta o número de mulheres pós-menopáusicas na nossa sociedade, aumenta também a importância da prevenção de fragilidade, do envelhecimento ativo e de uma boa qualidade de vida. Assim, devido à grande importância social e ao impacto em todo o mundo, a saúde da mulher e consequentemente a menopausa, tornou-se um campo em rápida expansão na necessidade de investigação científica. Assim, para ajudar e tornar as intervenções mais eficazes, tornou-se essencial avaliar a investigação sobre intervenções ou programas que visam a promoção da saúde durante este estágio fisiologicamente complexo.

Por conseguinte, o principal objetivo desta tese foi analisar a interação das características da menopausa com o exercício e aptidão física, de forma a avaliar as intensidades ideais de exercício cardiovascular; e também, examinar os efeitos deste programa de 12 meses de exercício multicomponente na composição corporal. Acreditamos que o conhecimento de tais interações contribuiria para uma prescrição de exercício mais adequada por parte dos profissionais de fitness e médicos. De referir que, esta tese está incluída no projeto de "Menopausa em Forma" – um estudo randomizado, controlado aprovado pela Fundação para a ciência e tecnologia – que tem como objetivo desenvolver a promoção de exercício e saúde na mulher pós-menopáusica através de um programa de exercício moderado-a-vigoroso de 12 meses (combinando step aeróbica, força muscular e flexibilidade/controlo postural).

Os resultados sugerem uma diminuição da aptidão cardiorrespiratória com o aumento da idade e do tempo decorrido desde a menopausa, mas especialmente na presença de adiposidade central e total ou ainda na presença de reduzido índice músculo-esquelético. Contudo, a análise ao programa de exercício (de 12 meses de duração e intensidade moderada-a-vigorosa) revela que este foi capaz de influenciar, de forma positiva e significativamente, todas as variáveis antropométricas e de composição corporal, juntamente com a taxa metabólica basal. Mais ainda, não foram encontrados efeitos interativos entre o exercício e as características da menopausa, sugerindo que o exercício por si só pode promover melhorias na composição corporal de mulheres na pós-menopausa. Os dados analisados revelaram ainda que, o valor de 40% da FCR no limite inferior está fortemente relacionado com o primeiro limiar ventilatório mas, que o limite superior de 84% (proposto pelo ACSM) sobrestima o valor de %FCR ao segundo limiar ventilatório, sugerindo que, a zona alvo de treino cardiorrespiratório para esta população deva ser mais estreita (40% -70% FCR) do que a recomendada para a população em geral. Os nossos resultados demonstraram ainda que (relativamente à composição corporal das mulheres na pós-menopáusicas) parece ser desnecessário ajustar a prescrição do exercício às características individuais da menopausa – sugerindo assim que programas de exercício com características semelhantes às descritas no “Menopausa em Forma” devem ser recomendados e oferecidos às mulheres pós-menopáusicas para a promoção da saúde e bem-estar.

Palavras-chave: Aptidão aeróbica, Composição corporal, Características da Menopausa, Pós-menopausa, Programa de exercício, Diretrizes, Limiares ventilatórios
Chapter 1: General Introduction
Introduction

Today, most women live long enough to become menopausal. According to projections of national surveys (INE, 2008, 2013), life expectancy for Portuguese women more than doubled in less than 100 years (1920–2012), from 40 to 82.59 years. This means that approximately one-third of women’s lives will be lived in postmenopause.

As the number of postmenopausal women in our society increases, so does the significance of the prevention of frailty, active aging, and quality of life. Thus, due to the great social importance and impact worldwide, women’s health and menopause became a rapidly expanding field in need of scientific investigation.

Menopause is a significant event in most women’s lives, since it marks the end of natural reproductive life. It is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity, and it is recognized to have occurred after 12 consecutive months of amenorrhea (Sherman, 2005). During the transition from the fertile years through menopause and beyond, a woman experiences many physical and psychological changes. Most of these changes are normal consequences of both menopause and aging. Alongside, there are associated simultaneous social and cultural behavior changes (e.g., parental care giving, children leaving home, and preparation for retirement) that increase the tendency among postmenopausal women (PM) to become sedentary, to change body composition, and to gain weight.

Consequently, this period is usually associated with health complaints, a decrease in quality of life, and an increase in risk for illnesses, especially osteoporosis and coronary heart diseases (Blair et al., 1996). As a matter of fact, at this time point, a marked increase in the incidence of total body and visceral fat (Van Pelt, Evans, Schechtman, Ehsani, & Kohrt, 2002), sarcopenia (Visvanathan & Chapman, 2010), type 2 diabetes, dyslipidemia, hypertension (ACSM, 2010), and metabolic syndrome (LaMonte et al., 2005; Royer et al., 2007) is observed. Excessive fat deposition, particularly when located within the abdominal cavity, has been also associated with an increased risk of insulin resistance, pro-inflammatory profile, and some forms of cancer (Tchernof & Despres, 2013). PM also experience a progressive reduction of lean body mass (Lynch, Ryan, Berman, Sorkin, & Nicklas, 2002; Ross & Katzmarzyk, 2003) and cardiorespiratory fitness (Lynch et al., 2002). Menopause may also influence substrate utilization, as higher circulating levels of FSH are associated with lower whole body fat oxidation and energy expenditure during exercise (Abildgaard et al., 2013). Therefore, menopause can increase morbidity and mortality from many causes, and particularly from cardiovascular diseases.

Moreover, if a woman undergoes menopause at an earlier age, she could become even more susceptible to serious illnesses and rapid senescence with an increasing number of various limitations and disabilities, reducing her chances of living an independent life until death. As a result, age at menopause is suggested to be a potent biological marker of women’s aging, and an average age at menopause could be associated with greater longevity (Tom, Cooper, Patel, & Guralnik, 2012); revealing that menopausal and PM clearly
have health needs that are different from those of younger women, and different from males of the same age range.

Though each woman’s menopause experience is unique, the greatest differences observed are between women who have natural menopause and those whose menopause is early or induced (Bhattacharya & Jha, 2010; North American Menopause Society, 2010). Whether the postmenopausal years are spent without compromised mental, physical, and social functions not only depends on the lifestyle adopted in the younger years, but perhaps equally so on the lifestyle adopted around the time of menopause (Poehlman, 2002).

Hormone therapy (HT) is the treatment of choice to alleviate physical symptoms associated with the menopause and to help prevent the clinical consequences of an estrogen deficient state. However, controversy still remains due to the differences in length, intensity, and type of hormone therapy and also whether HT alone can induce significant changes in total body composition over time (Asikainen, Kukkonen-Harjula, & Miilunpalo, 2004; Castelo-Branco et al., 2003; O'Donnell, Kirwan, & Goodman, 2009; Teixeira et al., 2003; Yuksel et al., 2007). On the other hand, exercise programs might be a useful treatment in reducing or alleviating the symptoms of menopause, particularly given that there is already convincing evidence that it can attenuate most of the negative consequences of the menopausal transition on body composition, physical fitness, and overall health (Daley, Stokes-Lampard, & Macarthur, 2009; Roussel et al., 2009). Examples of these also include reduced depression (Villaverde Gutierrez et al., 2012) and fatigue and the preservation of bone density (Asikainen et al., 2004).

However, low exercise participation rates have been reported in PM (Daley et al., 2007). Plus, though from a public health perspective, much research has been conducted highlighting the benefits of physical activity (ACSM, 2010; Garber et al., 2011; Nelson et al., 2007), only a small fraction (Asikainen et al., 2004; Daley et al., 2013; Reed et al., 2014) reports to the effects of structured exercise programs designed specifically to attain PM characteristics and needs.

Physicians and fitness professionals need effective interventions and guidelines to use when prescribing exercise care to women at this optimal time for implementing behavioral changes in preparation for healthy aging. Evaluating the research on interventions or programs that target health promotion during this physiologically complex stage is essential to help and guide into more effective interventions.

For that, this thesis is included, and only a small part of, the “Shape Up During Menopause” study – a randomized, controlled trial approved by the Portuguese Foundation for Science and Technology – that aims to develop exercise and health promotion in PM (Moreira, 2004). Unlike the majority of exercise programs that focus only on strict features (e.g., weight/waist circumference or bone mineral density/fall), the “Shape Up During Menopause” program is a 12-month moderate-to-vigorous exercise program (combining step aerobics, muscle strength, and flexibility/postural control training) aiming to improve overall health-related components of physical fitness and fall risk of PM (Moreira, 2004).
Assisting the “Shape Up During Menopause” program research team since its beginning and throughout all its years (2005-2014) raised intriguing questions (potentiated by some literature gap impression) about exercise and the postmenopausal period. But because questions lead to answers and answers lead to more questions, some of the initial and simpler interrogations that led to the central questions are present only in the published abstracts, book chapter, and oral presentations enumerated in the list of publications in the early pages of this document.

On a personal note, probably one of the first questions since the early beginning was, what were the effects of this 12-month multicomponent exercise program on the body composition of PM? (Study 2). Still nowadays, available research on this particular topic is surprisingly scarce, particularly research in which the effectiveness of a PM exercise program on the overall body composition variables is addressed (Asikainen et al., 2004). Also scarce are studies that examine body composition variables’ interaction with menopausal characteristics. As such, it was considered pertinent to study the interaction of menopause characteristics alongside the exercise and body composition (study 1 and 2). Therefore, knowledge of such interactions would help physicians and sport-science and fitness professionals move toward appropriate exercise prescription (study 2 and 4).

The American College of Sports Medicine (ACSM) has helped to identify the appropriate physical activity and exercise dosage recommendations and has suggested that cardiorespiratory and metabolic requirements are best achieved with exercise intensities ranging from moderate to vigorous (ACSM, 2010). However, studies reported that PM exhibit low exercise participation rates (Daley et al., 2007) and that higher intensities are associated with reduced pleasure or increased displeasure during the activities (Ekkekakis, Parfitt, & Petruzzello, 2011); and that higher intensities can also be less effective in treatment of hyperlipidemia and obesity (Nybo et al., 2010; Romijn et al., 1993). Hence, an accurate exercise intensity prescription is a key factor for exercise adherence and subsequently preserving physical fitness, as well as improving psychological well-being, self-esteem, and health practices.

Based on these reasons, it was also our purpose to examine PM heart rate reserve (HRR) percentage at first and second ventilatory thresholds (VT’s) and to compare it with the optimal intensity range recommended by the ACSM (40%-84%HRR); and also to evaluate whether a higher aerobic power level corresponded to a higher HRR at VT’s (study 3). At the same time, we have identified (while controlling for aging effect) whether menopausal characteristics could affect the physiological variables generally used to assess cardiorespiratory exercise prescription (study 4).

Moreover, known to irreversibly decline with age at different rates, it is unclear if the accelerated decline in maximal oxygen uptake (VO_{2max}) during the menopause transition could also be a result of reduced estrogen production and deleterious changes in body composition (Ades & Toth, 2005; Hollenberg, Yang, Haight, & Tager, 2006; Stathokostas, Jacob-Johnson, Petrella, & Paterson, 2004). As VO_{2max} is a standard measure of cardiorespiratory fitness (CRF) and a key component for a good health (ACSM, 2010), it seemed pertinent to identify the effect of body composition and menopause characteristics in CRF of PM
General Introduction

(study 1). Especially since older women frequently experience a greater intra-abdominal fat deposition, a shift toward a more atherogenic lipid profile, oxidative stress, inflammatory markers, and cognitive impairment is usually associated with sarcopenia (Bauer & Sieber, 2008; Maltais, Desroches, & Dionne, 2009; Sites et al., 2002). Additionally, sarcopenic obese women have a higher risk of functional impairment and physical disability (Janssen, 2010; Zamboni, Mazzali, Fantin, Rossi, & Di Francesco, 2008).

Considering, therefore, the several questions raised, the aim of this thesis was to analyze the interaction of the menopausal characteristics with exercise and physical fitness, to evaluate optimal cardiovascular exercise intensities, and to examine the effects of this 12-month multicomponent exercise program on body composition. It is the author’s sincere believe that the responses to these problems will help physicians and fitness professionals improve the exercise prescription accuracy for this population.

This research project entitled “Exercise, body composition, cardiorespiratory fitness and menopausal characteristics: effects and interactions,” was supported by the Portuguese Science and Technology Foundation (FCT) by a doctoral grant (SFRH/BD/63984/2009). In the last four years, several works have been presented in International and National Scientific Meetings, and others have been published in Scientific Journals.

The Thesis has the following main chapters:

- Chapter 2 presents a global literature overview regarding menopausal transition and characteristics and aging process, particularly effects in body composition and CRF, as well as the benefits of exercise and physical activity.
- Chapter 3 includes four studies:
  - Study 1. Effects of body composition and menopause characteristics on maximum oxygen uptake of postmenopausal women.
  - Study 2. Effects of a 12-month multicomponent exercise program on the body composition of postmenopausal women – the “Shape Up During Menopause” program.
  - Study 3. The upper limit of the cardiorespiratory training zone (40-84%HRR) is overestimated for postmenopausal women.
  - Study 4. Should menopausal characteristics be considered during cardiorespiratory exercise prescription in postmenopausal women?
- Chapter 4 and Chapter 5 present a general discussion of the results obtained in the four independent studies; the main conclusions, practical application and overall limitations of the thesis are displayed.

Chapter 6 contains thesis bibliography.
References


General Introduction


Chapter 2: Literature overview
2.1. Menopause

The menopause, defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity, marks the end of natural female reproductive life. It is a period of rapid change in hormonal balance and can occur either naturally or as a result of medical or surgical intervention.

Natural menopause is commonly defined in the epidemiological literature to have occurred after 12 consecutive months of amenorrhea without an obvious intervening cause. It occurs with the final menstrual period, which is known with certainty only in retrospect a year or more after the event (Utian, 1999). The average age for the onset of natural menopause in women in the western world is 51 years, although it can commonly occur anywhere between 40 and 58 (North American Menopause Society, 2006). If menopause occurs before the age of 40, this is considered premature (Utian, 1999). The age at natural menopause has been consistently associated with race, ethnicity, and demographic and lifestyle factors (B. L. Harlow & Signorello, 2000; Mikkelsen, Graff-Iversen, Sundby, & Bjertness, 2007). Smoking, lower parity, and lower socioeconomic status have been found to be closely related with earlier menopause, an indicator of reduced longevity (Gold, 2011; Sun et al., 2012).

The available evidence regarding time elapsed since menopause (TM) reveals that the most significant menopausal changes caused by sexual hormone exhaustion occur during the first two years and that the stabilization period can last between three and six years after menopausal onset (S. D. Harlow et al., 2012) – thereby limiting the concentrations of estrogen and triggering an altered production of adipokines by the adipose tissue (especially intra-abdominal) with cardiovascular reflexes (Lee, Wu, & Fried, 2013).

Induced menopause, as opposed to natural, is defined as the cessation of menstruation abruptly caused by either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g., by chemotherapy or radiation) (Utian, 1999). Premenopausal women who experience induced menopause are therefore faced with menopause and its effects without the gradual adjustment time of perimenopause (time immediately prior to the menopause and the first year after menopause). Moreover, because women who experience induced menopause are often younger, they also spend more years without the benefits of estrogen and are at greater risk for some health problems more frequent later in life, such as osteoporosis and heart disease (North American Menopause Society, 2006). Symptoms related to induced menopause can be similar to those from natural menopause, including hot flashes, sleep disturbances, and vaginal dryness. However, the abrupt loss of estrogen in induced menopause can result in more sudden and intense symptoms (North American Menopause Society, 2006; Topatan & Yildiz, 2012).

2.2. Hormone Therapy

Hormone therapy (HT) is commonly used in women to treat/alleviate menopause-related vasomotor symptoms and their potential consequences, such as diminished sleep quality, irritability, poor
concentration, osteoporosis in women at high risk of fracture, and subsequently a reduced quality of life (de Villiers et al., 2013; North American Menopause Society, 2012). HT has also been associated (when added to exercise) with some positive changes in body composition and CRF (Castelo-Branco et al., 2003; Mercuro et al., 2007; Yuksel et al., 2007).

However, there is a growing body of evidence that HT formulation, route of administration, and the timing of therapy produces different effects. Thus, due to the differences in length (duration), intensity (dosage and route of administration), timing, and type of HT (e.g., estrogen, estrogen-progestogen, bioidentical hormones) some literature results/benefits are ambiguous (O'Donnell et al., 2009; Perez-Lopez, Chedraui, Gilbert, & Perez-Roncero, 2009; Szymanski, Kessler, & Fernhall, 2005; Teixeira et al., 2003). Plus, benefit-risk ratio is a complex issue, since HT has been associated with an increased risk of breast and endometrial cancers (Sturdee et al., 2011). For this, postmenopausal HT has been undergoing thorough scrutiny in the last decade.

Though the debate surrounding it is controversial and ongoing, recent detailed revised guidelines were published and have been regularly updated by the major menopause societies (de Villiers et al., 2013; Lambrinoudaki et al., 2010; North American Menopause Society, 2012; Sturdee et al., 2011). The latest recommendations of use suggest that estrogen therapy (alone) is safer and that benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause.

### 2.3. Postmenopause, aging and body composition

Postmenopause is defined as the period dating from the final menstrual period, regardless of whether the menopause was induced or spontaneous (Utian, 1999).

The process of aging is known to influence body weight and body composition (Kuk, Saunders, Davidson, & Ross, 2009). However, in women, these changes seem to be enhanced with the onset of menopause (Misso et al., 2005).

As epidemiological studies suggest, menopause has numerous deleterious changes in body composition associated with it (Poehlman, 2002). Perhaps the most significant transformation is the increase of total body fat, alongside the shift in fat distribution – from a gynoid (gluteofemoral region) to an android pattern (trunk) (Tremollieres, Pouilles, & Ribot, 1996). Features of the visceral obesity include a pro-inflammatory profile characterized by increased levels of C-reactive protein, interleukin-6, tumor-necrosis factor-α (TNF-α) and reduced levels of adiponectin, the last a potentially anti-diabetic and anti-atherogenic adipokine. Thus, this modification in body composition is increasingly recognized as a strong independent predictor of insulin resistance, dyslipidemia (i.e., elevated triglycerides, small LDL cholesterol particles, and reduced HDL cholesterol) (Van Pelt et al., 2002), metabolic syndrome (Royer et al., 2007), inflammation, type 2 diabetes, and some types of cancer in PM (Tchernof & Despres, 2013).
Figure 1 - A proposed model by Vincent, Raiser, and Vincent (2012) of the contributing major factors to muscle mass insufficiency and sarcopenia in obese older adults (AOX, antioxidant; IGF, insulin like growth factor; IMAT, intramuscular adipose tissue; IL-1, interleukin 1; IL-6, interleukin 6; TNF-α, tumor necrosis factor α; CRP, C reactive protein). + denotes a positive effect on the downstream variable.

Adding associated hypertension and obesity, these transformation are a certain major risk factor for cardiovascular disease, increasing the risk of disability and all-cause mortality. Plus, obesity also has substantial psychosocial consequences. Since it affects appearance, self-esteem, and social functioning, depression and depressive symptoms are common among obese PM.

Moreover, the deficiency of estrogen after menopause accelerates bone loss, and there is an increased incidence of osteoporotic fractures in PM (Deroo & Korach, 2006). Also, the confluence of aging and obesity may create an ideal environment for skeletal muscle catabolism and decline in physical function, contributing to musculoskeletal degenerative disorders (such as osteoarthritis – a highly disabling degenerative disease of the joints) (Hughes et al., 2001) and the development of sarcopenia (Vincent et al., 2012). Sarcopenia is characterized by progressive and generalized loss of skeletal muscle mass (Cruz-Jentoft et al., 2010). The coexistence of diminished muscle mass and increased fat mass is being called ‘sarcopenic obesity’ or, more recently, “sarcobesity” (Parr, Coffey, & Hawley, 2013). Sarcopenic obese PM present a higher loading in the plantar surface during the stance phase comparing with non-sarcopenic
non-obese, a fact that might limit their basic daily activity tasks, such as walking (Monteiro, Gabriel, Aranha, et al., 2010). Accordingly, sarcopenic obesity is characterized by a higher risk of functional impairment and physical disability (Janssen, 2010; Zamboni et al., 2008), low functional fitness (Moreira et al., 2008), gait and balance deficits (Waters, Hale, Grant, Herbison, & Goulding, 2010), and increased cardiovascular risk. Still, when considered together, obesity per se contributes more to a lower physical capacity than sarcopenia (Bouchard, Dionne, & Brochu, 2009; Jankowski et al., 2008; Rolland et al., 2009).

2.4. Postmenopause, aging and cardiorespiratory fitness

Maximum oxygen uptake (VO$_{2\text{max}}$) is determined by the capacity of the cardiovascular system to provide oxygenated blood to the working muscles, as reflected in maximal cardiac output (Q$_{\text{max}}$), and the capacity of the working muscle to extract oxygen from the blood, as manifested by arterial-venous oxygen content difference (ACSM, 2010). Thus, VO$_{2\text{max}}$ is recognized as the international reference standard for CRF and is typically expressed in mL.kg$^{-1}$.min$^{-1}$ allowing for meaningful comparisons among individuals with differing body weight (V. H. Heyward, 2010).

CRF reports the ability to perform dynamic exercise using large muscle mass at moderate to high intensity for prolonged periods (ACSM, 2010). Higher levels of CRF are associated with higher levels of habitual physical activity and exercise, which in turn are associated with many health benefits (ACSM, 2010). On the other hand, as well as presenting challenges to physical independence and quality of life, low CRF has been consistently associated with increased risk of premature death from all causes and specifically from cardiovascular diseases (ACSM, 2010; Ross & Katzmarzyk, 2003).

An age-related decline in CRF has been observed in both longitudinal and cross-sectional studies (Ades & Toth, 2005; Hawkins, Marcell, Jaque, & Wiswell, 2001; Hawkins & Wiswell, 2003; Kenny, Yardley, Martineau, & Jay, 2008; Stathokostas et al., 2004; Stathokostas, Kowalchuk, Petrella, & Paterson, 2009). Aging, however, is inevitable, and literature supports an age-related decline in VO$_{2\text{max}}$ at a rate of approximately 10% per decade from age 30 (Hawkins & Wiswell, 2003; Hollenberg et al., 2006). This decline in VO$_{2\text{max}}$ seems to be a consequence of both central (inability to increase the cardiac output and stroke volume and particularly reductions in maximal heart rate (HR$_{\text{max}}$)) and peripheral (narrowed arterial-venous oxygen difference) adaptations (Hawkins et al., 2001; Hawkins & Wiswell, 2003; Murias, Kowalchuk, & Paterson, 2010; Zarins et al., 2009). Furthermore, a worsened peripheral arterial flow (due to an increase in local vascular resistance instigated by the reduced level of estrogen and nitric oxide) was found in healthy postmenopausal subjects in comparison with fertile women of the same age (Mercuro, Longu, Zoncu, & Cherchi, 1999). Though exercise does not influence in HR$_{\text{max}}$, it may help to improve/maintain lean body mass, and it may also result in greater cardiac output and larger stroke volume – variables associated with higher VO$_{2\text{max}}$ (Hawkins & Wiswell, 2003; McCole et al., 2000). However, current evidence supports that high-intensity exercise may reduce this loss of VO$_{2\text{max}}$ by up to 50% in young and middle-aged men but not women. The fact by which PM do not appear to be able to
reduce loss rates to less than 10% per decade can be related to estrogen status (Hawkins et al., 2001; Hawkins & Wiswell, 2003). Plus, as mentioned, PM show a worsened arterial vasodilation response, mainly due to the reduced levels of nitric oxide (Herrington, Braden, Williams, & Morgan, 1994); and menopause is also associated with a decrease in exercise tolerance (Mercuro et al., 2006).

Additionally, CRF is also negatively correlated with common body composition alterations caused by age and menopause transition, such as elevated body mass index, waist circumference, total and central adiposity (Abdulnour et al., 2010; Lynch et al., 2002), and reduced skeletal muscle mass and strength (Hepple, Hagen, Krause, & Jackson, 2003; Maltais et al., 2009). Moreover, there is an atrophy and denervation of type 2 fibers and a shift of muscle fibers toward type 1 fibers, rendering older individuals weaker and slower (Maltais et al., 2009).

Although the beneficial effect of HT is still controversial, some authors state that estrogen therapy is associated with a better CRF when combined with exercise (Green et al., 2002), some say that this higher VO$_{2\text{max}}$ is independent from physical activity (Mercuro et al., 2007), and others proclaim that these effects are not clear or significant (McCole et al., 1999; O'Donnell et al., 2009; Stathokostas, Kowalchuk, Petrella, & Paterson, 2008; Szymanski et al., 2005; Uusi-Rasi, Beck, Sievänen, Heinonen, & Vuori, 2003).

### 2.5. Exercise and physical activity

Levels of physical activity decrease with age (Milanovic et al., 2013) and are a risk factor for many serious diseases. In fact, type 2 diabetes, cardiovascular diseases, colon cancer, breast cancer, dementia, and depression constitute a cluster of diseases, recently defined as “diseasome of physical inactivity” (Pedersen, 2009). Another consequence of the aging process and decreased physical activity is a declining stimulus of the physiological systems that cause structural and functional changes in skeletal muscle. These modifications are associated with muscle weakness, reduced endurance capacity, and insulin resistance (Kenny et al., 2008; Nair, 2005; Weiss, Spina, Holloszy, & Ehsani, 2006).

Thus, oddly, even though meeting the recommendations of physical activity is reflected in numerous health benefits (ACSM, 2010), this does not seem to be usual behavior in developed societies (European Commission, 2014; Troiano et al., 2008).

Recent data obtained by accelerometry in representative samples of Portuguese adults indicate that physical inactivity is highly prevalent in elder but especially in middle-aged women (Baptista et al., 2012).

Moreover, it is known that menopausal transition is accompanied with a decline in energy expenditure mainly associated with a decrease in physical activity and a shift to a more sedentary lifestyle (Duval et al., 2013). Still, women who pass menopause face many changes that may lead to loss of health-related fitness, especially if sedentary (Asikainen et al., 2004).
Regular physical activity and exercise are associated with numerous physical and mental health benefits in men and women. Accordingly, exercise training is strongly recommended in PM to tussle the “diseasome of physical inactivity”, since it reduces the risk of developing coronary heart disease, stroke, obesity, type 2 diabetes, and some forms of cancer (e.g., colon and breast cancers) (ACSM, 2010; Garber et al., 2011).

Similarly of particular relevance for PM (table 1), exercise preserves bone mineral density, preserves skeletal muscle mass, and reduces the risk of falling (Bolton et al., 2012; Karaarslan et al., 2010; Vincent et al., 2012). Also, it has been suggested that physical activity may have a beneficial effect on reducing vasomotor symptoms in menopausal women (Daley et al., 2009), which is of particular importance given the HT risk-benefit controversy.

Table 1 - Effects of exercise on menopausal symptoms (adapted from Perez and Garber (2011))

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Effect of Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>Helps maintain weight or promote weight loss via increased caloric expenditure</td>
</tr>
<tr>
<td>Abdominal fat</td>
<td>Decreased visceral fat independent of weight loss</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>↓hypertension, ↓triglycerides, ↓LDLs, ↓weight, ↓waist circumference, and ↓insulin resistance</td>
</tr>
<tr>
<td>Bone health</td>
<td>Reduces bone loss</td>
</tr>
<tr>
<td>Mental health</td>
<td>Increases quality of life, reduces depression and anxiety, and enhances cognitive function</td>
</tr>
<tr>
<td>Hot flashes (vasomotor symptoms)</td>
<td>May help control mild hot flashes</td>
</tr>
<tr>
<td>Urogenital atrophy or incontinence</td>
<td>Strengthen the pelvic floor muscles</td>
</tr>
</tbody>
</table>

Consistent with the recommendations of ACSM (and attending to the risk factors that are normally associated with menopausal transition: central obesity, dyslipidemia, hypertension, hyperglycemia), PM seeking to improve their health and well-being should perform aerobic (cardiovascular endurance) exercises that involve large muscle mass groups (ACSM, 2010; V. H. Heyward, 2010), preferentially every day for 30 to 60 minutes at a moderate-to-vigorous intensity (until 59% heart rate reserve in hypertensive patients). To maximize effects on bone density and skeletal muscle mass, weight-bearing cardiorespiratory exercise (e.g., walking) should be included in a program of exercise for the PM. This aerobic exercise should be complemented (2–3 d.wk⁻¹) with a strength (enhance of muscle protein synthesis in myofibrils) and resistance training program (increase in the activity of mitochondrial oxidative enzymes) (Short, Vittone, Bigelow, Proctor, & Nair, 2004) at moderate-vigorous intensity (i.e., 60%-80% 1-RM, 8 to 12 repetitions) (ACSM, 2010; Nelson et al., 2007; Perez & Garber, 2011; Dennis R Taaffe, 2006).

Also, (as stretching of each of the major muscle-tendon groups helps to improve and maintain range of movement of a joint) flexibility exercises should be performed on at least 2 to 3 days per week; as well as neuromotor exercises that incorporate balance, agility, and coordination, which facilitate engaging in activities of daily living and may help to reduce falls (ACSM, 2010; Perez & Garber, 2011).
Literature overview

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Literature overview


Chapter 3: Experimental Studies
Study 1. Effects of body composition and menopause characteristics on maximal oxygen uptake of postmenopausal women
Study 1

Abstract

Objective: The aim of this study was to identify the effects of body composition and menopause characteristics on maximal oxygen uptake (VO\(_{2\text{max}}\)) variation in postmenopausal women.

Methods: The study was conducted on 208 healthy women aged 49 to 79 years. Data related to menopause were obtained through medical history. Measurements of fat mass, visceral fat area, skeletal muscle mass (SM), fat-free mass, and basal metabolic rate were assessed by octopolar bioimpedance. SM index was calculated using the formula \( SM \text{ index} = \frac{SM}{\text{weight}} \times 100 \), and VO\(_{2\text{max}}\) was assessed through a modified Bruce protocol.

Results: Cardiorespiratory fitness was negatively associated with age, percent fat mass, visceral fat area, body fat-muscular condition and central adiposity-muscular condition. Only time elapsed since menopause revealed a statistically significant correlation with VO\(_{2\text{max}}\). Age and time of menopause aside, body fat-muscular condition was related to the VO\(_{2\text{max}}\) variation, presenting an interactive effect with basal metabolic rate. Central adiposity-muscular condition also affects VO\(_{2\text{max}}\); however, the association of all interactions, age, basal metabolic rate and time elapsed since menopause was not significant.

Conclusions: Our data suggest an impairment of cardiorespiratory fitness with increasing age and time elapsed since menopause, but especially in the presence of increased total and central adiposity or reduced SM index. Body fat-muscular condition groups were significant related to the VO\(_{2\text{max}}\) variation, regardless of age and time elapsed since menopause but not of basal metabolic rate. Central adiposity-muscular condition was a significant and independent factor on the VO\(_{2\text{max}}\) exercise related variations.

Key words: Cardiorespiratory fitness, Body composition, Characteristics of menopause, Postmenopausal women
Introduction

Cardiorespiratory fitness (CRF) is the ability to perform dynamic exercise, using large-muscle mass, at moderate to high intensity for prolonged periods, and is a key component for a good health (ACSM, 2010).

For older adults, this is particularly significant given the well-reported age effect. The maximal oxygen consumption ($V_{O2\text{max}}$) is known to decline with age at a rate of approximately 10% per decade from age 30 years (Ades & Toth, 2005; Hawkins & Wiswell, 2003; Hollenberg et al., 2006; Kenny et al., 2008; Stathokostas et al., 2004; Weiss et al., 2006). Current evidence suggests that in middle-aged and older postmenopausal women (PM), the $V_{O2\text{max}}$ rate loss could also be related to estrogen status (Hawkins & Wiswell, 2003). However, it is unknown if this accelerated decline in $V_{O2\text{max}}$ during the menopause transition could be also a result of reduced estrogen production. The role of hormonal therapy (HT) is also unclear. Whereas some authors state that estrogen therapy is associated with a better CRF when combined with exercise (Green et al., 2002), some say that this higher $V_{O2\text{max}}$ is independent from physical activity (Mercuro et al., 2007), and others proclaim that these effects are not clear or significant (McCole et al., 1999; O'Donnell et al., 2009; Stathokostas et al., 2008; Szymanski et al., 2005; Uusi-Rasis et al., 2003).

Other important changes occur during menopause. Low levels of CRF combined with the several hormonal changes in the menopause transition are associated with an increased total body and visceral fat mass (FM) (Lynch et al., 2002; Ross & Katzmarzyk, 2003), metabolic syndrome (LaMonte et al., 2005), risk of other cardiovascular diseases (Blair et al., 1996), and progressive reduction in lean tissue, which can be countered with exercise (Hagberg et al., 2000; Lebrun et al., 2006; Lynch et al., 2002; Ross & Katzmarzyk, 2003). Whereas some authors (Lynch et al., 2002; Ross & Katzmarzyk, 2003; Toth, Gardner, Ades, & Poehlman, 1994) announce that the loss of fat-free mass (FFM) and the increase in adiposity contribute to a decline in the peak of VO$_2$, others (Hollenberg et al., 2006) state that this rate of decline is independent from baseline variables such as body composition (e.g., lean body mass, lean/fat ratio).

To our knowledge, no study has examined the combined effects of body fat–muscular condition and central adiposity-muscular condition in CRF variation of PM. Knowledge of such interactions could be very useful in the definition and implementation of preventive and therapeutic strategies for healthy aging. Therefore, the purpose of this study was to identify the effects of body composition and menopause characteristics on maximum oxygen uptake in PM.

Methods

Sample

A sample of women were recruited through advertising from the surrounding community into the “Shape Up During Menopause” study. There were 300 women participating in the program; however, after
discarding missing values, dropouts, and outliers, the final sample was reduced to 208 healthy PM participants (mean ± SD: age, 57.60 ± 6.62 y; weight, 68.90 ± 11.59 kg; height 155.09 ± 0.05 cm, 157 women had undergone natural menopause, and 51 induced menopause (North American Menopause Society, 2010)).

This randomized controlled trial was approved by the Portuguese Foundation for Science and Technology and designed to examine the effects of exercise in cardiovascular risk, fall risk and physical fitness in PM (Moreira, 2004). Ninety-four of these women were taking HT and 114 did not use any HT.

Before inclusion into the study, the reproductive and medical history of each woman was collected, and an informative written consent was obtained. None of the women had premature menopause (North American Menopause Society, 2010), and the elements of inclusion depended on some factors, namely, (1) the absence of a significant hepatic, hematological and renal disease; (2) the inexistence of cardiovascular diseases (symptoms of angina pectoris or myocardial infarction in the last 3 months) or uncontrolled hypertension (systolic arterial pressure superior to 200 mmHg and diastolic superior to 105 mmHg); (3) the non-use of β-blockers and anti-arrhythmic agents and; (4) the inexistence of skeletal-muscle conditions that may alter one’s participation in the exercise or may present aggravated symptoms in its execution.

The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Trás-os-Montes and Alto Douro.

**Anthropometry/Body composition**

Height (H) was determined by the stadiometer (SECA 220; Seca Corporation, Hamburg, Germany), and weight (W), skeletal muscle mass (SM), visceral fat area (VFA), FFM, and FM were evaluated by an octopolar bioimpedance (InBody 720; Biospace, Seoul, Korea), complying with the preparation standards specified in the literature (Biospace Co, 2004; Chumlea & Sun, 2005; V. H. Heyward & Wagner, 2004). The basal metabolic rate (BMR) was assessed using the Cunningham (1991) equation, and the skeletal muscle mass index (SMI) was calculated using the formula proposed by Janssen et al (2002): SMI= (SM/W) x 100. The measurements were performed in the morning, after an overnight fast, and by the same technician. The cutoff points to obesity and elevated VFA were, respectively, an FM of 35% or greater (Lohman & Going, 1998), and VFA of 100 cm² or greater (Despres & Lamarche, 1993; Williams et al., 1996), and sarcopenia was considered present if SMI was 28% or less (Janssen et al., 2002).

Technical errors of variables were determined by two repeated measures, in a subgroup of ten PM (W, 0.06 kg; H, 0.09 cm; SM, 0.21 kg; VFA, 0.97 cm²; FFM, 0.20 kg; FM, 0.32 kg; BMR, 7.66 kcal.day⁻¹).
Experimental Studies

**Cardiorespiratory fitness**

\( \text{VO}_{2\text{max}} \) was assessed using a modified Bruce protocol (Bruce, Kusumi, & Hosmer, 1973), typically used for elderly or sedentary individuals (Vivian H. Heyward, 2004). The submaximal test was conducted on a treadmill (Panatta Sport, Apiro, Italy), up until an 85% value of maximal heart rate. Expired gases were analyzed continuously during all exercise protocol using a gas analyzer (Sensormedics 2900C; SensorMedics Corporation, Yorba Linda, USA). The initial 3-minute stage occurred at a speed of 2.74 km.h\(^{-1}\) and 0% gradient. The second and third stages had the same speed and duration of 5% and 10% gradient, respectively. Each subsequent stage exhibited an increment of 1.28 km.h\(^{-1}\) in speed and 2% in gradient. \( \text{VO}_{2\text{max}} \) was predicted using a linear regression of the mean heart rate and \( \text{VO}_{2} \) values of the last minute of each stage, between 55% and 85% of predicted maximum heart rate.

The participants had been instructed to maintain their usual medications, and the preparation norms included the use of comfortable sportswear, the restriction of intense exercise the previous day, and abstinence from smoking and alcohol consumption 12 hours before the test, along with no food intake 2 hours before to the evaluation (Vivian H. Heyward, 2004).

**Statistical analysis**

Statistical analyses were conducted using the Statistical Package for the Social Sciences program (version 17.0; SPSS Inc., Chicago, IL) and a 5% of statistical significance was established. Measures of central tendency and distribution were examined to describe the sample, to test for homoscedasticity and to describe outcomes. Normality of distribution was checked using Shapiro-Wilk’s and Kolmogorov-Smirnov tests. The association between \( \text{VO}_{2\text{max}} \) and other variables were assessed by the Pearson’s correlation analyses. Factorial analysis of variance was used to study the effects and interaction of body fat-muscular condition and central adiposity-muscular condition in CRF outcomes. All undergoing assumptions to inferential analyses were taken. Finally, independent-sample \( t \) tests were used to compare the CRF in the prior established groups of obesity and VFA according to the muscular condition and the different groups of age (≤57 and >57 y), time of menopause (TM; <10 y and ≥10 y) and BMR (<1238 and ≥1238 kcal.day\(^{-1}\)). Cohen’s effect sizes were used to identify the magnitude of the identified differences (Nakagawa & Cuthill, 2007). The Dunn-Šidák procedure was used to perform multiple comparisons and protect against type I errors (Ludbrook, 1991).

**Results**

The characteristics of the 208 asymptomatic PM, with an average age of 57.57 years, are presented in Table 1. The \( \text{VO}_{2\text{max}} \) values ranged between 16.39 and 48.31 mL.kg\(^{-1}\).min\(^{-1}\) with a mean value of 29.14 ± 5.68 mL.kg\(^{-1}\).min\(^{-1}\). At an average of 1258.76 kcal.day\(^{-1}\), the amplitude of the BMR was 518 kcal.day\(^{-1}\). Most
of the women presented a normal muscular condition (91.8%) and elevated values of %FM (74%) and VFA (89.9%).

Maximum oxygen uptake was negatively associated (p≤0.01) with age (r = -0.30), and especially with VFA (r = -0.53), %FM (r = -0.48), body fat-muscular condition (r = -0.40) and central adiposity-muscular condition (r = -0.37). SMI displayed a moderate and positive correlation with VO\textsubscript{2max} (r = 0.48, p≤0.01). Concerning the menopause characteristics, only TM revealed a significant, although weak, correlation with dependent variable (r = -0.26, p≤0.01).

Study 1: Table 1 - Baseline characteristics of the sample (n=208)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.57 ± 6.62</td>
<td>40.60 – 79.68</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.90 ± 11.59</td>
<td>45.80 – 108.70</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.09 ± 5.39</td>
<td>142.00 – 170.00</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>27.74 ± 8.71</td>
<td>9.10 – 55.70</td>
</tr>
<tr>
<td>Fat Mass (%)</td>
<td>39.34 ± 6.92</td>
<td>17.90 – 53.00</td>
</tr>
<tr>
<td>Fat-Free Mass (kg)</td>
<td>41.17 ± 4.85</td>
<td>30.40 – 54.40</td>
</tr>
<tr>
<td>Visceral Fat Area (cm\textsuperscript{2})</td>
<td>133.61 ± 27.28</td>
<td>52.10 – 206.10</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>22.40 ± 2.93</td>
<td>15.80 – 30.40</td>
</tr>
<tr>
<td>Skeletal Muscle Mass Index (%)</td>
<td>32.89 ± 3.78</td>
<td>25.66 – 45.98</td>
</tr>
<tr>
<td>Basal Metabolic Rate (kcal.day\textsuperscript{-1})</td>
<td>1258.76 ± 104.72</td>
<td>1027.00 – 1545.00</td>
</tr>
<tr>
<td>Maximum Oxygen Uptake (mL.kg\textsuperscript{-1}.min\textsuperscript{-1})</td>
<td>29.14 ± 5.68</td>
<td>16.39 – 48.31</td>
</tr>
</tbody>
</table>

Table 2 presents the effects of body fat-muscular condition and central adiposity-muscular condition and the interaction of these factors with age, BMR and TM in VO\textsubscript{2max} of PM. Age and TM aside, body fat-muscular condition influenced (p<0.01) the variation of CRF of these women, presenting an interactive effect with BMR (p=0.015).

Study 1: Table 2 - Simple effects and interactions of Factorial ANOVA comparing the variation of VO\textsubscript{2max} of postmenopausal women according to body fat-muscular condition and central adiposity-muscular condition with age (≤ 57 y and >57 y, BMR (< 1238 kcal.day\textsuperscript{-1} and ≥ 1238 kcal.day\textsuperscript{-1}) and time of menopause (< 10 y and ≥ 10 y).

<table>
<thead>
<tr>
<th>Factors</th>
<th>Interactions</th>
<th>Tukey HSD Mean Difference (effect size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO\textsubscript{2max}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Fat-Muscular Condition</td>
<td>F= 19.5**</td>
<td>NONSA vs ONSA ** (0.84)</td>
</tr>
<tr>
<td>Model 1</td>
<td>F= 3.3</td>
<td>ONSA vs OSA * (0.67)</td>
</tr>
<tr>
<td>Model 2</td>
<td>F= 17.7**</td>
<td>NONSA vs OSA** (1.39)</td>
</tr>
<tr>
<td>Model 3</td>
<td>F= 19.9**</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>F= 0.7</td>
<td></td>
</tr>
<tr>
<td>BMR</td>
<td>F= 2.9</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>F= 4.3*</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Adiposity-Muscular Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>F= 13.6**</td>
<td>NVFNSA vs EVFNSA ** (1.10)</td>
</tr>
<tr>
<td>Model 2</td>
<td>F= 5.0</td>
<td>NVFNSA vs EVFNSA** (1.93)</td>
</tr>
<tr>
<td>Model 3</td>
<td>F= 14.1**</td>
<td>EVFNSA vs EVFSA ** (0.75)</td>
</tr>
<tr>
<td>Age</td>
<td>F= 1.8</td>
<td></td>
</tr>
<tr>
<td>BMR</td>
<td>F= 0.4</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>F= 1.1</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: NONSA, non-obese and non-sarcopenic; ONSA, obese and non-sarcopenic; OSA, obese and sarcopenic; NVFNSA, normal visceral fat area and non-sarcopenic; EVFNSA, elevated visceral fat area and non-sarcopenic; EVFSA, elevated visceral fat area and sarcopenic; BMR, basal metabolic rate; HSD, honestly significant; ANOVA, analysis of variance; VO\textsubscript{2max}, maximum oxygen consumption; *p ≤ 0.05; **p ≤ 0.01;
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The post hoc test revealed that women in the nonsarcopenic and nonobese group (NONSA) exhibited higher \( \text{VO}_{2\max} \) values compared with obese and nonsarcopenic (ONSA) women and obese and sarcopenic (OSA) women (+4.40 and +7.73 mL.kg\(^{-1}\).min\(^{-1}\), respectively, p<0.05). ONSA women presented an average increase of 3.33 mL.kg\(^{-1}\).min\(^{-1}\) (p<0.05) compared with obese women with sarcopenia. Likewise, women with a normal VFA and muscular condition presented better (p<0.05) \( \text{VO}_{2\max} \) values when compared with elevated VFA and nonsarcopenic (EVFNSA) women and elevated VFA and sarcopenic (EVFSA) women, with increases of 5.82 and 9.75 mL.kg\(^{-1}\).min\(^{-1}\), respectively. Also, when VFA was 100 cm\(^2\) or greater, women with a normal muscular condition exhibited better CRF levels (3.93; p=0.01) than did EVFSA women.

Multiple comparisons revealed that when BMR was considered, the \( \text{VO}_{2\max} \) differs only in obese ONSA, presenting better CRF when BMR was 1238 kcal.day\(^{-1}\) or greater (Study 1: Figure 1). The central adiposity-muscular condition affected the variation of \( \text{VO}_{2\max} \) (p<0.01), but interactions with age, BMR and TM were not significant (Table 4).

![Study 1: Figure 1 - Variation of maximum oxygen uptake according to body fat-muscular condition and basal metabolic rate groups (NONSA, non-obese and non-sarcopenic; ONSA, obese and non-sarcopenic; OSA, obese and sarcopenic). Legend: * denotes statistical significant interaction.](image)

When TM and BMR cutoffs points were considered (Table 3), the NONSA and OSA women presented no differences in \( \text{VO}_{2\max} \) values. When age was accounted for, no differences were detected in OSA group (p=0.971). In the presence of a normal muscular condition and regardless of obesity (p=0.013 and p=0.038, respectively), older women presented lower CRF values. The women in ONSA group with fewer TM and higher levels of BMR revealed better \( \text{VO}_{2\max} \) values, contrary to those with TM of 10 years or more (29.59
and 26.62 mL·kg$^{-1}$·min$^{-1}$, respectively, $p=0.001$) and BMR less than 1238 kcal·day$^{-1}$ (29.14 and 27.30 mL·kg$^{-1}$·min$^{-1}$, respectively, $p=0.031$).

**Study 1: Table 3** - Comparison of mean values of maximum oxygen uptake in three groups of postmenopausal women according to body fat and muscular condition.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>NONSA</th>
<th>ONSA</th>
<th>OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>P (ES)</td>
<td>n</td>
</tr>
<tr>
<td>Age</td>
<td>≤ 57 yrs</td>
<td>28</td>
<td>34.25 ± 5.12 (0.58)</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>&gt; 57 yrs</td>
<td>26</td>
<td>30.98 ± 6.13</td>
<td>74</td>
</tr>
<tr>
<td>Basal Metabolic Rate</td>
<td>&lt; 1238 kcal·day$^{-1}$</td>
<td>29</td>
<td>33.84 ± 4.64 NS</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>≥ 1238 kcal·day$^{-1}$</td>
<td>25</td>
<td>31.31 ± 6.78</td>
<td>72</td>
</tr>
<tr>
<td>Time of Menopause</td>
<td>&lt; 10 yrs</td>
<td>34</td>
<td>31.70 ± 5.92 NS</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>≥ 10 yrs</td>
<td>20</td>
<td>31.70 ± 5.92</td>
<td>61</td>
</tr>
</tbody>
</table>

Results from independent samples t-test. | Legend: NONSA, non-obese and non-sarcopenic; ONSA, obese and non-sarcopenic; OSA, obese and sarcopenic; ES effect size; NS, non-significant;

The comparison of the average maximum oxygen uptake values, based on three groups of central adiposity-muscular condition, is shown in Table 4. In EVFNSA group, women with a menopause duration of less than 10 years and age 57 years or younger exhibited better CRF levels compared to older women and superior TM ($p=0.009$). No significant differences were observed between the means of remaining variables.

**Discussion**

This study was designed to identify the effect of body composition and menopause characteristics in CRF of PM. To our knowledge, this is the first study to investigate, in this specific population, the effects of muscular condition and its association with body fat or central adiposity in VO$_{2\text{max}}$. Data revealed an impairment of CRF with the increasing of age and TM, but especially when related to total and central adiposity or reduced SMI. When the interactive effects of body fat-muscular condition with age, BMR and
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TM were analyzed, only BMR affected the variation of VO\textsubscript{2max}. Furthermore, our results indicated that the central adiposity-muscular condition had a significant effect on the variation of VO\textsubscript{2max}. The women 57 years or younger in the ONSA and EVFNSA groups and with TM less than 10 years

Obesity is recognized as one of the most important underlying risk factors for a wide variety of diseases, including hypertension, dyslipidemia, diabetes mellitus, venous thromboembolism, stroke, breast and gynecological cancer and osteoarthritis, and also as being related to a higher expression of climacteric symptoms (Castelo-Branco et al., 2009; Lambrinoudaki et al., 2010). Most women with estrogen deficiency, and early menopause (Shuster, Rhodes, Gostout, Grossardt, & Rocca, 2010) exhibit three or more cardiovascular risk factors (Royer et al., 2007; Vardugina & Azarenkova, 2010). Several factors can contribute to the increased prevalence of obesity in PM, such as age, increased lipoprotein lipase in abdominal and gluteal adipocytes (Ferrara, Lynch, Nicklas, Ryan, & Berman, 2002), decreased lipolysis (Ferrara et al., 2002; Mastorakos, Valsamakis, Paltoglou, & Creatsas, 2010), reduced physical activity and energy expenditure (Keller et al., 2010; Teede, Lombard, & Deeks, 2010), increase in caloric intake (Mastorakos et al., 2010), variation in hormonal patterns (Sutton-Tyrrell et al., 2010), higher rates of depression and anxiety, use of antidepressant medication, life events that occur during the life transition of menopause (Keller et al., 2010), and attitude and perception of weight and weight management (Muennig, Jia, Lee, & Lubetkin, 2008). In the present study most of the women (74%) showed obesity and all had a VFA of 100 cm\textsuperscript{2} or greater.

The group of women who showed a decline in strength and functional quality of muscle in addition to the loss of muscle protein mass (Abellan van Kan, 2009) presented levels of FM of 48,80% or greater and VFA of 133.70 cm\textsuperscript{2} or greater. This could be due to increased adiposity, especially central adiposity which is associated with a decreased effect of insulin on protein synthesis (Roubenoff & Hughes, 2000) and a higher production of proinflammatory cytokines, like tumor necrosis factor and interleukin-6, resulting in an increase of protein catabolism (Rolland & Vellas, 2009).

Sarcopenic obese women have a higher risk of functional impairment and physical disability (Janssen, 2010; Zamboni et al., 2008), low functional fitness (Moreira et al., 2008), gait and balance deficits (Waters et al., 2010), increased CVD risk (Stephen & Janssen, 2009), higher peak pressure, and absolute impulses in the midfoot (Monteiro, Gabriel, Aranha, et al., 2010) among others. Nonetheless, recent studies state that when considered together, obesity per se contributes more to a lower physical capacity than sarcopenia (Bouchard et al., 2009; Jankowski et al., 2008; Rolland et al., 2009). Maximal oxygen uptake is a valid proxy of functional capacity of the heart and lungs, and is well accepted as the standard measure of CRF (ACSM, 2010). Known to irreversibly decline with age (Ades & Toth, 2005; Hawkins & Wiswell, 2003; Hollenberg et al., 2006; Kenny et al., 2008; Statthokostas et al., 2004; Weiss et al., 2006) at different rates, VO\textsubscript{2max} has been associated with cardiovascular diseases and premature death (Blair et al., 1996; Despres & Lamarche, 1993). In our sample, 80 women presented a fitness level lower than 40% and 34 presented higher than 80% of age-predicted (ACSM, 2010) peak maximal aerobic power.
Our data suggest that the deterioration of the muscular condition (SMI) and the increase of adiposity (especially central) could seriously compromise the aerobic capacity (revealing a greater association with these variables than that with age). However, the minor association of VO\textsubscript{2max} with age compared to body composition variables could be due to the cohort age distribution (56.7% with 50–59 years). The data are supported by previous studies on the age effect in VO\textsubscript{2} (Ades & Toth, 2005; Hawkins & Wiswell, 2003; Hollenberg et al., 2006; Kenny et al., 2008; Stathokostas et al., 2004; Weiss et al., 2006) and the role of SMI (Janssen, 2010; Moreira et al., 2008; Stephen & Janssen, 2009; Zamboni et al., 2008), FFM and body fat (Abdulnour et al., 2010; Ross & Katzmarzyk, 2003; Toth et al., 1994) in CRF.

The available evidence about the effects of menopause characteristics, such as menopausal status, time and nature of menopause or HT on CRF is insufficient and contradictory. For some authors (McCole et al., 1999; Mercuro et al., 2007), estrogen deficiency and nitric oxide reduction, are the main factors responsible for the impairment of arterial vasodilation and peripheral vascular reactivity (Mercuro et al., 2007), which is negatively related to CRF. Although it is usually accepted that natural menopause and HT are normally associated to less abrupt estrogen reductions when compared to surgical menopause and absence of HT, there is much unanimity in ascribing an enhanced physical performance in HT users. Therefore, some authors state that HT is associated with a better CRF, independently (Mercuro et al., 2007) or combined with exercise (Green et al., 2002), and others believe that these effects are not clear or significant (McCole et al., 1999; O'Donnell et al., 2009; Stathokostas et al., 2008; Szymanski et al., 2005; Uusi-Rasi et al., 2003). These disagreements are probably due to the different estrogen types and doses used and to exercise program characteristics. In our data, TM was the only menopause variable with a significant correlation with VO\textsubscript{2max}, being the women with more than 10 years of TM those who exhibited lower CRF ranks. Although the effect of menopause duration in CRF has not yet been considered in literature, the few studies (Lynch et al., 2002; Mercuro et al., 2006, 2007; Poehlman, 2002) that investigated the effect of the menopausal status in CRF, state that this could be related to a worsened arterial vasodilatation response in healthy PM when compared with premenopausal women. Moreover, all index values of upper body fat distribution were found to be more strongly correlated with years since menopause than with age (Tremollieres et al., 1996). The observed increase in the present study of FM and android fat distribution in PM, might explain in part, the worsening cardiovascular risk associated with estrogen deficiency. In addition, because the type of HT was not recorded and because TM was expressed as an ordinal variable (≤10 years and > 10 years), the lack of effect of the first variable and the effect of the second should be interpreted with caution.

The present study demonstrated that, regardless of age and TM, the combination of %FM with %SMI shows a significant effect on the variation of the VO\textsubscript{2max}, thus indicating a more important role of body composition in the aerobic fitness variation of PM. As expected, non sarcopenic and non-obese women exhibited higher CRF levels compared to those in ONSA and OSA groups.

Interestingly, when BMR and the previous combinations (body fat-SMI) were consided, this interaction revealed a combined effect on the VO\textsubscript{2max} values, but only in ONSA women with a BMR of 1238 kcal.day\textsuperscript{-1}.
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or greater. The lack of effect of TM might be related to the categorization of this variable in two groups, with a very similar number of participants in each one.

Structural and functional changes in skeletal muscle (reduction in muscle mass and muscle fibers, and a shift of muscle fibers toward type 1 fibers) in addition to a declining stimulus of the physiological systems from decreased physical activity, occur during the aging process. These modifications are associated with muscle weakness, reduced endurance capacity, and insulin resistance (Kenny et al., 2008; Nair, 2005; Weiss et al., 2006). As expected, the comparison of CRF within each of the groups formed on the basis of the %FM and %SMI, according to age, TM and BMR cutoff points, revealed that regardless of the women being obese, younger PM exhibit better VO\textsubscript{2max} compared with women aged 57 years or older (p = 0.013 and p = 0.038 respectively). Also, the presence of a TM less than 10 years and a BMR of 1238 kcal.day\textsuperscript{-1} or greater seems to positively affect the VO\textsubscript{2max} in obese women. One possible reason to explain the absence of mean differences in the OSA group could be the reduced sample size.

Furthermore, our results indicated that the combination of central adiposity-muscular condition is independent of age, BMR and TM, displaying an isolated effect in VO\textsubscript{2max}, the dependent variable. Accordingly, the women with a normal VFA and muscular condition in this study presented better VO\textsubscript{2max} values compared with the women in the EVFNSA and EVFSA groups. Still, when the central adiposity-muscular condition groups were confronted with the age, TM and BMR divisions, it was clear that in presence of elevated visceral fat, women who were older and had larger TM revealed greater VO\textsubscript{2max} deterioration.

Consequently, these results are particularly significant, considering the previously referred gaps and paradoxes of the interface of body composition (Hollenberg et al., 2006; Toth et al., 1994) and characteristics of menopause (Green et al., 2002; Hawkins & Wiswell, 2003; McCole et al., 1999; Mercuro et al., 2007; O’Donnell et al., 2009; Statthokostas et al., 2008; Szymanski et al., 2005) in the VO\textsubscript{2max} variation. Knowledge of such interactions would help physicians and sport science and fitness professionals to provide appropriate exercise prescription (Hankinson et al., 2010). Attending to the risk factors that are normally associated with central obesity (dyslipidemia, hypertension, hyperglycemia), PM should perform aerobic (cardiovascular endurance) exercises that involve large muscle mass groups (ACSM, 2010), preferentially every day, for 30 to 60 minutes and at an intensity of 40% to 75% of the heart rate reserve (59% in hypertensive patients). This aerobic exercise should be complemented (2–3 d.wk\textsuperscript{-1}) with a strength (enhance of muscle protein synthesis in myofibrils) (Nair, 2005; Yarasheski et al., 1999) and resistance training program (increase in the activity of mitochondrial oxidative enzymes) (Short et al., 2004) at a moderate intensity (i.e., 60%-80% 1-repetition maximum, 8-12 repetitions) (ACSM, 2010; Nelson et al., 2007; Dennis R Taaffe, 2006). Because of their relevance, factors associated with lifestyle (e.g., smoking status, HT, and protein intake), should also be considered, supporting a multidisciplinary intervention.
Finally, some drawbacks should recognize, such as the absence of sarcopenic PM without obesity or with a normal VFA; only a small number of participants presented normal values of VFA and, simultaneously sarcopenia and obesity or elevated visceral fat area. These limitations might be due to the fact that sarcopenia is prevalent in older populations (Cruz-Jentoft et al., 2010) (the present study presents a relatively young adult sample), the lower physical activity and estrogen levels observed in this population (Moreira & Gabriel, 2010; Poehlman, 2002), and the menopausal tendency to increase body fat and central adiposity (Douchi et al., 2002; Poehlman, 2002). Lastly, the precision of body fat measurement by the InBody720 system is still not clarified in literature (Biospace Co, 2004; Gibson, Holmes, Desautels, Edmonds, & Nuudi, 2008; Medici et al., 2005; Volgyi et al., 2008).

Conclusions

In summary, the results of this study suggested an impairment of CRF with increasing age and TM, but especially in the presence of total and central adiposity or reduced SMI. Body fat-muscular condition groups were related with the VO$_{2\text{max}}$ variation, regardless of age and TM but not of the BMR. The central adiposity-muscular condition had a significant effect on the variation of VO$_{2\text{max}}$ and in ONSA and EVFNSA groups 57 years or younger and with TM less than 10 years, it manifests benefits on CRF.
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Bouchard, D. R., Dionne, I. J., & Brochu, M. (2009). Sarcopenic/obesity and physical capacity in older men and women: data from the Nutrition as a Determinant of Successful Aging (NuAge)-the Quebec longitudinal Study. *Obesity (Silver Spring), 17*(11), 2082-2088.


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Study 2. Effects of a 12-month multi-component exercise program on the body composition of postmenopausal women
Study 2

Abstract

**Objective:** The aims of this study were to identify the effects of a 12-month exercise program on the body composition of postmenopausal women and to examine the interaction of menopause characteristics (nature, time since menopause and hormone therapy) with exercise.

**Methods:** A total of 158 postmenopausal Caucasian women were analyzed in this study (70 in the control and 88 in the exercise group). This subset is part of the “Shape Up During Menopause” which is a program that aims to develop exercise and health promotion in postmenopausal women. Exercise and control groups were tested before and at the end of the program. Data related to menopause was obtained through medical history. Measurements of fat mass, visceral fat area, skeletal muscle mass, fat-free mass, soft lean mass, and basal metabolic rate were assessed by octopolar bioimpedance.

**Results:** Alongside basal metabolic rate, all the anthropometric and body composition variables were influenced by the exercise program. The major differences between groups were found in skeletal muscle mass, soft lean mass total, fat-free mass, and skeletal muscle mass index (effect sizes ranged from 0.89 to 6.64). There were no interactive effects found between exercise and menopause characteristics.

**Conclusions:** There were positive changes in all measured variables and no significant interactive effects with menopause characteristics; therefore, our data suggest that exercise alone promoted improvements in postmenopausal women’s body composition.

**Key words:** Exercise program, Menopause, Characteristics of menopause, Body composition, Fat mass, visceral fat, Sarcopenia, Physical Fitness
**Introduction**

Menopause is often characterized by many changes that may lead to the deterioration of women’s health-related fitness, especially in association with sedentary lifestyles (Asikainen et al., 2004). Available research has shown that postmenopausal women (PM) frequently present an increased incidence of risk factors for cardiovascular disease (Blair et al., 1996; Castelo-Branco et al., 2003). Also usually associated with metabolic syndrome (Royer et al., 2007) PM experience a progressive reduction of lean body mass and CRF (Lynch et al., 2002) and an increase of total body and visceral fat (Van Pelt et al., 2002), contributing largely to the increased rates of morbidity and mortality (Perez-Lopez et al., 2009). Combined with physical inactivity, the presence of elevated central adiposity, oxidative stress, inflammatory markers, and cognitive impairment or loss have been shown to be associated with sarcopenia (Bauer & Sieber, 2008; Maltais et al., 2009; Sites et al., 2002). It is also known that the combination of sarcopenia with increased fat mass generates a reduction in aerobic fitness levels (Aragao et al., 2011) and that sarcopenic obesity affects significantly the temporal characteristics of foot roll-over during walking in PM (Monteiro, Gabriel, Sousa, Castro, & Moreira, 2010).

However, the available research is scarce on whether menopause characteristics, such as the nature of menopause or the time elapsed since menopause (TM) can meaningfully influence body composition. Although there is a general agreement on the positive effects of hormone therapy, controversy still remains due to the differences in length, intensity, and type of hormone therapy and whether hormone therapy alone can induce significant changes in total body composition over time (Asikainen et al., 2004; Castelo-Branco et al., 2003; O'Donnell et al., 2009; Teixeira et al., 2003; Yuksel et al., 2007). On the other hand, exercise programs may attenuate most of the negative consequences of the menopausal transition on body composition, physical fitness, and overall health (Roussel et al., 2009). From a public health perspective, much research has been conducted highlighting the benefits of physical activity (ACSM, 2010; Nelson et al., 2007), but only a small fraction (Asikainen et al., 2004) reports the effects of structured exercise programs designed specifically to attain PM characteristics and needs. These studies reveal decreases in percent body fat and waist circumference (Velthuis, Schuit, Peeters, & Monninkhof, 2009) as well as improvements of muscle strength (Figueroa, Park, Seo, Sanchez-Gonzalez, & Baek, 2011), muscular endurance (ACSM, 2010), gait pattern (Monteiro, Gabriel, Sousa, Abrantes, & Moreira, 2011) and VO\textsubscript{2}\text{max} (O'Donnell et al., 2009).

Therefore, unlike the majority of exercise programs, which focus on particular features (e.g., weight/waist circumference, bone mineral density/fall-related fitness, and others), the “Shape Up During Menopause” program (Moreira, 2004) was developed by the University of Trás-os-Montes and Alto Douro, aiming to improve overall health-related components of physical fitness and fall risk of PM. This is a 12-month moderate-to-vigorous exercise program combining aerobic step, flexibility/postural control training as well as resistance training. Also, since bench step is a weight bearing exercise mode, it results in an
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Improvement in atherosclerotic risk factors and attenuates declines in bone mass in elderly women (Ohta et al., 2012). Thus, expecting beneficial effects in aerobic fitness, muscle mass and strength, and balance capacity in PM.

As a result, the purpose of the current study was to identify the effects of this multi-component training program on the body composition of PM. The study also aimed to examine the interaction of menopause characteristics with the exercise.

Methods

Study design

This study is included in the “Shape Up During Menopause” program, a randomized, controlled trial approved by the Portuguese Foundation for Science and Technology. It was designed to examine the effects of exercise on cardiovascular risk, fall risk, and physical fitness in PM (Moreira, 2004).

The study had a desired minimum power for the statistical tests of 0.80, with an effect size of 0.40 at the 0.05 level of significance. The minimum number of subjects required for the total sample was determined to be 111.

The sample was recruited in Vila Real County (Portugal), primarily through different advertising procedures (e.g. regional newspapers, leaflets, posters, internet, and others) and during a period of three months (from October to December of 2005).

Prior to the women’s inclusion into the study, the reproductive and medical history of each woman was collected, and an informative written consent was obtained. None of the women had premature menopause. The exclusion criteria were: (1) a significant hepatic, hematological, or renal disease; (2) the existence of cardiovascular diseases (symptoms of angina pectoris or myocardial infarction in the last 3 months) or uncontrolled hypertension (systolic arterial pressure level higher than 200 mmHg and diastolic arterial pressure level higher than 105 mmHg); (3) the use of β-blockers and antiarrhythmic agents; (4) the existence of skeletal muscle conditions, neuro-muscular or neuro-physiological diseases that could alter one’s participation in exercise or present aggravated symptoms in its execution.

After medical screening, 254 women were enrolled and each woman was assigned a code number. Participants were randomly assigned to either the control group or the experimental group, using a computerized system: n=132 and n=122, respectively. All participants were informed by letter or telephone about the random allocation before the intervention, and they agreed to maintain their baseline level of physical activity (if not assigned to exercise) for the length of the study and accept the randomization result. The control group continued with their usual activity and did not receive any prescribed intervention during this period. To reduce the dropout rate, a detailed explanation of individual
health and fitness status as well as posterior inclusion were guaranteed to control group participants after the 12-month period. Women in both groups were asked to maintain their usual diet.

After recruitment and admission to the study, data were collected at baseline and after 12 months (between March 2006 and July 2007). All assessments were performed by technically and scientifically trained evaluators with no knowledge of the participant’s group assignment. The evaluations were supervised by the researchers.

The study was carried out in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Trás-os-Montes and Alto Douro.

**Sample**

Of the 254 women enrolled and randomized, after discarding dropouts, missing values and outliers, the final sample was reduced to 158 healthy PM: 70 in the control group and 88 in the experimental group (Study 2: Figure 1). The average attendance rate at the exercise program was 83.4% ± 11.38%.

**Anthropometry/Body composition**

Height was determined by the stadiometer (SECA 220, Seca Corporation, Hamburg, Germany), and weight (W), skeletal muscle mass (SM), visceral fat area, fat-free mass (FFM), fat mass, as well as soft lean mass, total and regional (arms, trunk and legs), were evaluated by an octopolar bioimpedance InBody 720 (Biospace, Seoul, Korea), complying with preparation standards specified in the literature (V. H. Heyward, 2010).

Measurements were taken in the morning and after an overnight fast, by the same technician, and electronically imported into Excel using the software Lookin’Body 3.0 (Biospace, Seoul, Korea). The basal metabolic rate (BMR) was estimated by the formula \((370 + 21.6 \times \text{FFM})\) proposed by Cunningham (1991) and the skeletal muscle mass index was calculated using the formula recommended by Janssen et al. (2002): \(\text{SMI} = \frac{\text{SM}}{\text{W/height}^2}\) x 100. The cutoff point for obesity (Sardinha & Teixeira, 2000) using the body mass index (BMI = \(\frac{\text{W}}{\text{height}^2}\)) was 25.5 kg.m\(^{-2}\). Technical errors of variables were determined by two repeated measures, in a subgroup of 10 PM (weight, 0.06 kg; height, 0.09 cm; skeletal muscle mass, 0.21 kg; visceral fat area, 0.97 cm\(^2\); fat-free mass, 0.20 kg; soft lean mass, 0.35 kg; fat mass, 0.32 kg; basal metabolic rate, 7.66 kcal.day\(^{-1}\)).
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**Nutritional Assessment**

During the 12-month period, women were asked to maintain their usual dietary and daily exercise habits. All participants completed a 3-day food intake questionnaire (Lopes, Aro, Azevedo, Ramos, & Barros, 2007) at the beginning of our intervention. The 3-day dietary record included two non-consecutive weekdays and one weekend day and was planned and overseen by a nutritionist. Total energy intake was obtained using the software Food Processor Plus (version 7.0, ESHA Research, Salem, OR), adapted to Portuguese food (Lopes et al., 2007).

**Exercise Program**

During a 12-month period, the exercise group was asked to attend three non-consecutive sessions per week, supervised by the same previously trained instructors. Each session lasted 60 minutes and began with 10 minutes of warm-up including global and specific movements and static stretching. Afterwards and twice a week, there were 20 to 25 minutes of step training (programmed for a target heart rate range of 50% to 84% of heart rate reserve) followed by 20 to 25 minutes resistance training of two to four sets.
of 8 to 12 repetitions per exercise, at 70%-80% of 1 repetition maximum (RM), with 1 min rest between sets. After this, 5-minute cool down ended the session. Once a week, the step and resistance exercises were substituted by 45 min of flexibility/postural control.

The step exercise mobilized large muscles in a continuous and controlled form using the lowest level of the step platform (Reebok, Lancaster, UK). A variety of common steps were employed in a symmetrical choreography and the level of complexity was adjusted to the participants. Step combinations consisted of conventional “up, up, down, down” stepping patterns, alternating step knee-lift sequences, traveling across the top of the step, patterns facing and turning away from the step, and lateral lunge propulsion steps. The music cadence of sessions was set between 118 and 122 beats per minute. The intensity was increased every 2 to 3 weeks (e.g., new step routines, upper body involvement, and vigorous arm-pumping actions), and monitored by heart rate monitors (Polar Electro, Kempele, Finland) accordingly to exercise recommendations for postmenopausal women defined by Perez & Garber (Perez & Garber, 2011) and the American College of Sports Medicine guidelines (ACSM, 2010).

The step exercise focused on lower body muscles, particularly affected by aging and menopause (Hughes et al., 2001), and stimulated balance, coordination, reaction time, and plantar pressure, factors of great importance on fall-risk prevention and osteoporotic fractures (Province et al., 1995). The resistance exercise were adjusted according to literature guidelines for age (ACSM, 2010) and conditions such as sarcopenia (Dennis R Taaffe, 2006) and osteoporosis (ACSM, 2010). We included six exercises with emphasis on muscles with influence on balance and in fall prevention (knee extensors, hip, knee flexors; and dorsiflexors/plantar flexors) (Dennis R Taaffe, 2006) in conventional weight machines and free weights. The exercise group attended a 4-week familiarization period with the resistance training. Initially, lighter loads were used, and participants performed one set of 15 repetitions at 40% to 50% of 1 RM. Resistance was increased on the basis of the 1 RM assessed every 6 weeks, using the same equipment used for resistance training. The increases were also designed to maintain loads at 70% to 80% RM, according to strength gain and adaptation to training.

The flexibility training focused on the execution of static stretching (3-4 repetitions/10-30 seconds per cycle) (Nelson et al., 2007). The methodology for improving postural control included exercises that stimulated the major systems responsible for controlling and maintaining balance: visual (eyes open and closed, changing in the eye direction), vestibular (walking side-cut maneuver, rotation on the longitudinal axis, and changes on the position of head), and proprioceptive (use of irregular surfaces, changes in gait pattern and in base of support).

**Statistical Analysis**

To estimate the sample size required, power analyses were performed using G*Power statistical software (version 3.1; Kiel University, Kiel, Germany). Measures of central tendency and distribution were used to
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describe the groups and test for homoscedasticity. Normality of distribution was inspected using Shapiro-Wilk’s and Kolmogorov-Smirnov tests. Data transformations were carried out when appropriate (Hopkins, 2003). Levene’s test for equality of variances was used to test the homogeneity of variance between the groups.

The factorial analysis of covariance (ANCOVA) of the outcome with the baseline as covariate is the more appropriate technique for these kinds of studies (Dimitrov & Rumrill, 2003; Van Breukelen, 2006). This technique permits the identification of a treatment effect from the difference between treated and untreated groups measured before and after treatment. The factors included in the model were the menopause characteristics. Bonferroni correction was used to protect against type I errors. Effect size was calculated and considered as defined by Cohen (1988), of 0.1, 0.25, and 0.4 as small, medium, and large effects respectively. All statistical analyses were performed using the Statistical Package for the Social Sciences software (version 17.0; SPSS Inc., Chicago, IL), and 5% significance was established.

Results

At baseline, the control and exercise groups were similar in age, menopausal characteristics and also in all the measured body composition variables (Study 2: Table 1). The range of age of the 158 women studied was 42-68 years, with a mean age of 56.90 ± 4.96 vs 55.44 ± 5.11 years in the control and exercise groups, respectively. The global mean weight was 67.95 ± 11.22 kg and the global mean height was 155.43 ± 5.25 cm. Sample mean BMI was 28.23 ± 4.65 kg.m⁻² (18.80 - 41.70 kg.m⁻²). Of all women, one hundred and seventeen (74.1%) were considered obese (Sardinha & Teixeira, 2000), by presenting a BMI ≥ 25.5 kg.m⁻².

Study 2: Table 1 - General anthropometric characteristics of the participants in the exercise and control groups. Data are given mean ± standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Control (n=70)</th>
<th>Exercise (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>68.57±10.92</td>
<td>68.29±10.58</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.16±5.41</td>
<td>155.05±5.39</td>
</tr>
<tr>
<td>Body Mass Index (kg.m⁻²)</td>
<td>28.64±4.93</td>
<td>28.39±4.61</td>
</tr>
<tr>
<td>Fat Mass (Kg)</td>
<td>27.54±8.40</td>
<td>28.58±8.24</td>
</tr>
<tr>
<td>Fat Mass (%)</td>
<td>39.24±7.04</td>
<td>41.35±6.46</td>
</tr>
<tr>
<td>Fat-Free Mass (kg)</td>
<td>41.04±4.78</td>
<td>39.71±4.32</td>
</tr>
<tr>
<td>Visceral Fat Area (cm²)</td>
<td>131.16±24.69</td>
<td>134.98±22.11</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>22.32±2.90</td>
<td>21.54±2.62</td>
</tr>
<tr>
<td>Skeletal Muscle Mass Index (%)</td>
<td>32.91±3.95</td>
<td>31.89±3.62</td>
</tr>
<tr>
<td>Soft Lean Mass (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft Lean Mass Total</td>
<td>38.71±4.56</td>
<td>37.45±4.17</td>
</tr>
<tr>
<td>Soft Lean Mass Arms</td>
<td>4.49±0.78</td>
<td>4.23±0.72</td>
</tr>
<tr>
<td>Soft Lean Mass Trunk</td>
<td>19.45±2.32</td>
<td>18.80±1.72</td>
</tr>
<tr>
<td>Soft Lean Mass Legs</td>
<td>11.95±1.78</td>
<td>11.81±1.58</td>
</tr>
<tr>
<td>Basal Metabolic Rate (kcal.day⁻¹)</td>
<td>1255.91±103.29</td>
<td>1211.66±161.72</td>
</tr>
</tbody>
</table>
Forty-two PM of the total cohort experienced an induced menopause and 116 a natural menopause (North American Menopause Society, 2010). The majority (63.9%) displayed a TM less than 10 years and 58% reported the use of HT. Time of menopause (65.7% vs. 62.5% with TM<10 years), nature of menopause (74.3% vs 72.7% with natural menopause), HT (60% vs. 55.7% used hormone therapy). Also, no significant differences were found between groups for total energy intake (1997.28 ± 409.95 kcal.day−1 vs. 2104.79 ± 507.07 kcal.day−1).

Table 2 shows the effects of the intervention on body composition and basal metabolic rate. Alongside basal metabolic rate, all anthropometric and body composition variables were influenced by the exercise program. Revealing only large effects (effect size ranged from 0.89 to 6.64), the major differences between groups were found in skeletal muscle mass, soft lean mass total, fat-free mass and skeletal muscle mass index. Additionally, the difference in the % fat mass was higher than in visceral fat. Regarding the regional soft lean mass, the trunk and arms subdivisions exhibited the greater modification (effect size of -4.17% and -3.69%, respectively).

**Study 2: Table 2 - Comparison between control and exercise groups in post-test, when controlling for baseline differences (ANCOVA models). Data are given as mean ± standard error (SE)**

<table>
<thead>
<tr>
<th>Post Test Variables</th>
<th>Control Group (N=70)</th>
<th>Exercise Group (N=88)</th>
<th>Difference (SE)</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>67.53±0.51</td>
<td>68.46±0.46</td>
<td>-0.94 (0.68)*</td>
<td>-1.94</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.31±0.22</td>
<td>156.04±0.20</td>
<td>-0.73 (0.30)*</td>
<td>-3.51</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>27.75±0.53</td>
<td>27.30±0.49</td>
<td>0.45 (0.70)*</td>
<td>0.89</td>
</tr>
<tr>
<td>Fat Mass (%)</td>
<td>40.56±0.48</td>
<td>38.84±0.43</td>
<td>1.71 (0.64)*</td>
<td>3.82</td>
</tr>
<tr>
<td>Fat-Free Mass (kg)</td>
<td>39.72±0.32</td>
<td>41.22±0.28</td>
<td>-1.50 (0.42)*</td>
<td>-5.06</td>
</tr>
<tr>
<td>Visceral Fat Area (cm²)</td>
<td>133.97±1.47</td>
<td>129.80±1.32</td>
<td>4.16 (1.96)*</td>
<td>3.02</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>21.56±0.11</td>
<td>22.25±0.10</td>
<td>-0.69 (0.15)*</td>
<td>-6.64</td>
</tr>
<tr>
<td>Skeletal Muscle Mass Index (%)</td>
<td>32.19±0.22</td>
<td>33.08±0.20</td>
<td>-0.90 (0.20)*</td>
<td>-4.28</td>
</tr>
<tr>
<td>Soft Lean Mass (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft Lean Mass Total</td>
<td>37.44±0.22</td>
<td>38.62±0.20</td>
<td>-1.18 (0.30)*</td>
<td>-5.68</td>
</tr>
<tr>
<td>Soft Lean Mass Arms</td>
<td>4.25±0.03</td>
<td>4.36±0.03</td>
<td>-0.12 (0.04)*</td>
<td>-3.69</td>
</tr>
<tr>
<td>Soft Lean Mass Trunk</td>
<td>18.84±0.09</td>
<td>19.19±0.08</td>
<td>-0.34 (0.12)*</td>
<td>-4.17</td>
</tr>
<tr>
<td>Soft Lean Mass Legs</td>
<td>11.73±0.10</td>
<td>12.02±0.09</td>
<td>-0.29 (0.14)*</td>
<td>-3.07</td>
</tr>
<tr>
<td>Basal Metabolic Rate (kcal.day⁻¹)</td>
<td>1212.64±11.08</td>
<td>1252.61±9.87</td>
<td>-39.98 (14.81)*</td>
<td>-3.86</td>
</tr>
</tbody>
</table>

*P<0.001

Furthermore, no interactive effects were found between the exercise and menopause characteristics (Table 3).
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Study 2: Table 3 - Analysis of exercise and menopausal characteristics effects in body composition and basal metabolic rate, when controlling for baseline differences (ANCOVA models)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nature of Menopause (natural vs induced)</th>
<th>Hormone Therapy (users vs non-users)</th>
<th>Time of Menopause (&lt;10 yrs vs ≥ 10 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>P</td>
<td>F</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.4 †</td>
<td>0.510</td>
<td>0.0 †</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.4</td>
<td>0.534</td>
<td>0.0</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>0.4 †</td>
<td>0.518</td>
<td>1.1</td>
</tr>
<tr>
<td>Fat Mass (%)</td>
<td>3.1</td>
<td>0.081</td>
<td>0.0 †</td>
</tr>
<tr>
<td>Fat-Free Mass (kg)</td>
<td>2.3</td>
<td>0.130</td>
<td>0.8</td>
</tr>
<tr>
<td>Visceral Fat Area (cm²)</td>
<td>1.2</td>
<td>0.275</td>
<td>1.1</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>0.6</td>
<td>0.443</td>
<td>0.7</td>
</tr>
<tr>
<td>Skeletal Muscle Mass Index (%)</td>
<td>0.9</td>
<td>0.334</td>
<td>0.0 †</td>
</tr>
<tr>
<td>Soft Lean Mass (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft Lean Mass Total</td>
<td>0.5</td>
<td>0.494</td>
<td>0.2</td>
</tr>
<tr>
<td>Soft Lean Mass Arms</td>
<td>0.4</td>
<td>0.506</td>
<td>0.0</td>
</tr>
<tr>
<td>Soft Lean Mass trunk</td>
<td>0.6</td>
<td>0.433</td>
<td>0.0</td>
</tr>
<tr>
<td>Soft Lean Mass Legs</td>
<td>0.6</td>
<td>0.435</td>
<td>0.6</td>
</tr>
<tr>
<td>Basal Metabolic Rate (kcal.day⁻¹)</td>
<td>0.2</td>
<td>0.652</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Transformations towards the normal distribution of variables: * square root, † logarithmic and ‡ reciprocal.

Discussion

The purpose of this study was to identify the effects of this 12-month moderate-to-vigorous exercise program, (combining step aerobics, muscle strength, and flexibility/postural control training) on the body composition of PM. An additional purpose was to examine the interaction of menopause characteristics with the exercise. The primary findings of this study confirmed our initial hypothesis that, along with BMR, all the anthropometric and body composition variables were influenced by the exercise program. Results showed significant improvements over time in the body composition of the exercise group, with meaningful positive changes in all variables with the exception of body weight. Furthermore, no significant interactive effects were found between the exercise and menopausal characteristics.

Available research on this particular topic is scarce (Asikainen et al., 2004), particularly research in which the effectiveness of an exercise program for PM on the overall body composition variables is addressed. Also scarce are studies that examine the variables’ interaction with menopausal characteristics.

This exercise program, combining step aerobics, muscle strength, and flexibility/postural control training, resulted in strong positive effects in total body fat, muscle mass, lean mass, and central adiposity of PM. However, because muscle mass is denser and heavier than the lost body fat, the program did not result in weight loss, which is consistent with literature (Ballor & Keese, 1991; Velthuis et al., 2009). Hypothetically, it is possible that this increase in the body weight of the exercise group could reflect an improvement of the mineral bone condition. This may result from the higher ground reaction forces and enhancement of the osteogenic stimulus prompted by the increase of SM. Acknowledged for osteonal bone formation, the use of a 15 cm (height) step platform can generate ground reaction forces beyond 1.5 × body weight (Burr, Martin, & Martin, 1983), alternating between 1.6 × body weight in the basic step
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and 1.99 × body weight in repeaters (Farrington & Dyson, 1995). Moreover, abdominal obesity has been shown to be a better indicator than body weight for identifying individuals at higher risk of developing chronic disease, which highlights the relevance of our findings (Canoy et al., 2007).

Displaying purely large effects (effect size ranged from 0.89 to 6.64), the major differences between groups were found in skeletal muscle mass, soft lean mass total, fat-free mass and skeletal muscle mass index. Also, the differences in visceral fat were higher than in fat mass (kg), reflecting, relatively to subcutaneous areas, a greater visceral adipocytes metabolic activity, sensitivity to lipolysis, and more insulin-resistant (Ibrahim, 2010). Many studies have suggested that even small variations in the amount of visceral fat can modify the risk of coronary heart disease in older individuals and consequently improve their quality of life (Schousboe et al., 2008; Teede et al., 2010). Likewise, central adiposity reduction has significant implications for the muscular and mineral condition of PM. Causes for these trends may include changes favoring decreased insulin resistance (Sites et al., 2002), and muscle anabolism (Maltais et al., 2009) and the limitation of the protein catabolism caused by leptin and proinflammatory cytokines (Schrager et al., 2007). Moreover, although 74.1% of the participants in this study were considered obese (Sardinha & Teixeira, 2000), this is in fact representative of the age group of the Portuguese female population, since a recent national study verified that more than two thirds of the Portuguese population is currently overweight or obese (Sardinha et al., 2012).

Interestingly, concerning the regional soft lean mass, the trunk and arm subdivisions exhibited the greatest modification. It appears that the benefits from the “Shape Up During Menopause” exercise program, regarding soft lean mass, are better reflected by the upper body, especially the trunk. Nonetheless, the leg’s soft lean mass also indicated a significant gain after the step and resistance training program, a gain that helps to preserve an independent living at old age and to reduce a powerful risk factor of morbidity and mortality (Rantanen, 2003). Also related to the improvement of the soft lean mass trunk and a good functional capacity is the increase of height values in the exercise group. Height loss is common with advancing age and is caused by curvature of the spine, narrowing of intervertebral discs, and vertebral fractures (Briot, Legrand, Pouchain, Monnier, & Roux, 2010). Postmenopausal women who have sustained a ≥3 cm height reduction compared with those who have maintained height, have an about fivefold the risk of spine fracture (Gunnes, Lehmann, Mellstrom, & Johnell, 1996).

The mechanisms by which this “Shape Up during Menopause” exercise program favorably influences the overall body composition, may be related with the inclusion of both aerobic and resistance training. Aerobic training increases the activity of mitochondrial oxidative enzymes in muscle, enhances protein synthesis (Short et al., 2004), improves lipid and carbohydrate metabolism (V. H. Heyward, 2010) and reduces total and abdominal adiposity (Alberga, Sigal, & Kenny, 2010), especially at vigorous intensities (Slentz et al., 2005). On the other hand, resistance training develops bone mass, fat-free mass, and functional performance (Alberga et al., 2010; V. H. Heyward, 2010; Maltais et al., 2009). Therefore, the present study also reinforces previous research confirming that exercise programs designed to improve
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body composition of PM, should include both aerobic and strength training (Alberga et al., 2010; V. H. Heyward, 2010; Maltais et al., 2009).

Furthermore, no significant interactive effects were found between exercise and any menopausal characteristics, suggesting an isolated influence of exercise in body composition improvements. Though it is difficult to compare our results with those of others, overall our results are in agreement with those reported in a recent meta-analysis suggesting that such exercise programs can improve body composition (Asikainen et al., 2004). The present findings also provide continued support for exercise alone promoting improvements in these endpoints.

Finally, some drawbacks should be recognized. Firstly, there is undoubtedly some selection bias since individuals who volunteer for a study may possess different characteristics than the average individual in the target population. Simultaneously, fitness tests and test results alone may have served to motivate women of control group to increase daily physical activity, affecting the body composition of this group. In future studies, we plan to control PM daily nutrition and physical activity before, during and after the exercise program. We will use food questionnaires and accelerometers.

Practical application

The results of this study may lead to endorsement that exercise programs with similar doses should be offered to women interested in this type of program. As recommended by the latest guidelines of the American College of Sports Medicine (ACSM, 2010) and recent research (Aragao et al., 2011), referring to the risk factors that are normally associated with central obesity (dyslipidemia, hypertension, hyperglycemia), PM should perform aerobic (cardiovascular endurance) exercises that involve large muscle mass groups (ACSM, 2010; V. H. Heyward, 2010), preferentially every day for 30-60 minutes at a moderate-to-vigorous intensity (until 59% heart rate reserve in hypertensive patients). This aerobic exercise should be complemented (2–3 d.wk⁻¹) with a strength (enhance of muscle protein synthesis in myofibrils) and resistance training program (increase in the activity of mitochondrial oxidative enzymes) (Short et al., 2004) at moderate-vigorous intensity (i.e., 60%-80% 1-RM, 8 to 12 repetitions) (ACSM, 2010; Nelson et al., 2007; Perez & Garber, 2011; Dennis R Taaffe, 2006).

In addition, regarding PM body composition, it seems to be unnecessary to make specific adjustments in the exercise prescription due to the individual menopausal characteristics. Furthermore, a multidisciplinary approach should be always considered key in the search for a healthy body and lifestyle. Knowledge of such interactions would help physicians and sport-science and fitness professionals move toward appropriate exercise prescription.
Conclusions

The results of the present study identify that a 12-month moderate-to-vigorous exercise program, (combining step aerobics, muscle strength, and flexibility/postural control training) influence all the anthropometric and body composition variables along with the basal metabolic rate. Results show significant improvements over time in the exercise-group body composition, with meaningful positive changes in all variables with the exception of weight. Furthermore, no interactive effects were found between the exercise and menopausal characteristics, suggesting that exercise alone can promote improvements in postmenopausal women’s body composition.
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References


Study 3. The upper limit of the cardiorespiratory training zone (40-84%HRR) is overestimated for postmenopausal women
Experimental Studies

Study 3

Abstract

Objective: The purpose of this study was to examine the heart rate reserve (HRR) at first and second ventilatory thresholds (VT’s) in postmenopausal women and compare it with optimal intensity range recommended by the ACSM (40%-84%HRR). An additional aim was to evaluate whether a higher aerobic power level corresponded to a higher HRR at VT’s.

Methods: Fifty-eight postmenopausal women participated in this study (aged 48-69). A graded 25W.min⁻² cycle ergometer (Monark E839) exercise protocol was performed in order to assess aerobic power. The heart rate and gas-exchange variables were measured continuously using a portable gas analyzer system (Cosmed K4b). The first (VT₁) and the second (VT₂) VT’s were determined by the time course curves of ventilation and O₂ and CO₂ ventilatory equivalents. A K-means clustering analysis was used in order to identify VO₂max groups (cut-off of 30.5 mL.kg⁻¹.min⁻¹) and differences were evaluated by an independent sample t-test. Bland-Altman plots were performed to illustrate the agreement between methods.

Results: The women’s HRR values at VT₁ were similar to 40%HRR in both VO₂max Groups. At VT₂ both VO₂max groups exhibited negative differences (p<0.01) for the predicted 84%HRR intensity (-14.46% in the lower VO₂max group and -16.32% in the higher VO₂max group).

Conclusions: An upper limit of 84% overestimates the %HRR value for the second ventilatory threshold, suggesting that the cardiorespiratory target zone for this population should be lower and narrower (40%-70%HRR).

Key words: Exercise intensity; Cardiorespiratory fitness; Heart rate reserve; Ventilatory threshold; Postmenopausal
Introduction

Physical activity and exercise are associated with numerous physical and mental health benefits. Recent recommendations from the American College of Sports Medicine (ACSM) have helped identify the appropriate physical activity dose recommendations. It is suggested that the cardiorespiratory and metabolic requirements are best achieved by exercise intensities ranging from moderate to vigorous (ACSM, 2010). Also, it is becoming increasingly clear that the exercise intensity dose is a key factor for exercise adherence, with higher intensities being associated with reduced pleasure or increased displeasure during the activities (ACSM, 2010; Ekkekakis et al., 2011) and being less effective in treatment of hyperlipidemia and obesity (Nybo et al., 2010; Romijn et al., 1993).

Heart rate (HR) is commonly used as a practical way of prescribing and monitoring exercise intensity. This data has often been expressed as a percentage of maximal heart rate (%HR\textsubscript{max}) or heart rate reserve (%HRR) (ACSM, 2010; Garber et al., 2011). The latest Position Statement from the ACSM recommends exercising at intensities ranging from 64\% to 95\% of HR\textsubscript{max} and 40\% to 89\% of HRR as lower and upper limits for prescription (Garber et al., 2011). However, in spite of a few exceptions, such as older adults, children, adolescents, pregnant women, and cardiac and other clinical situations, these current guidelines for exercise intensity are designed for a generally healthy population (ACSM, 2010; Garber et al., 2011; V. H. Heyward, 2010). Furthermore, these ranges of exercise intensity may not be appropriate for postmenopausal women (PM) (Church, Earnest, Skinner, & Blair, 2007), leading to supra-threshold intensities that can induce a higher anaerobic metabolism and reduced fat metabolism during exercise, an integrated psychobiological stress response, as well as turn the exercise into a very unpleasant activity (Ekkekakis et al., 2011).

A key topic of prescription is to select an exercise intensity that is adequate enough to stress the cardiovascular system without overtaxing it (V. H. Heyward, 2010). Hence, the relationship between the chosen physiological intensity parameter (e.g., heart rate reserve) as well as the aerobic and anaerobic thresholds is an important issue to consider. Exercise intensities between these thresholds can remain safe and effective for improving health and fitness and still remain pleasant (or at least tolerable) for most healthy individuals (Ekkekakis et al., 2011). In fact, these two concepts should be emphasized when setting an optimal exercise prescription, because the first threshold (aerobic) is related to a minimum desirable stimulus below which CRF does not easily improve, while the second threshold (anaerobic) represents a comfortable submaximal exercise intensity that can be used to set out the upper limit that is associated with a progressively reduced fat metabolism (ACSM, 2010). This is of particular significance for postmenopausal women, which combined with the several hormonal changes, have associated a progressive reduction in lean tissue, and increased total body and visceral fat mass (Lynch et al., 2002; Ross & Katzmarzyk, 2003), metabolic syndrome (LaMonte et al., 2005) and the risk of other cardiovascular diseases (Blair et al., 1996), which can and should be contradicted with exercise activity (Lynch et al., 2002; Ross & Katzmarzyk, 2003).
The continuous gas exchange data can be used to assess the aerobic and anaerobic thresholds in non-invasive procedures; thus, the use of ventilatory thresholds can be an important method to establish an optimal range of HR for exercise in PM (Blain, Meste, Bouchard, & Bermon, 2005; Cottin et al., 2006). Based on these reasons, the purpose of this study was to examine the heart rate reserve (HRR) at first and second ventilatory thresholds (VT’s) in postmenopausal women and compare it with optimal intensity range recommended by the ACSM (40%-84%HRR). An additional aim was to evaluate whether a higher level of VO$_{2\text{max}}$ corresponded to higher HRR at VT. The responses to these problems will help physicians and fitness professionals to improve the exercise prescription accuracy for this population.

Methods

Subjects and Experimental Design

Fifty-eight postmenopausal Caucasian women aged 48-69 years, were recruited from the surrounding community through advertising. Prior to inclusion in the study, a physician collected the reproductive and medical history of each woman and written informed consent was also obtained. All participants were apparently healthy and had neither neuromuscular nor neurophysiological diseases that could alter their participation in exercise or present aggravated symptoms in its execution. The overall mean duration of menopause for the women was 9.46 ± 5.70 years (95% CI from 7.94 to 10.97) and none reported premature menopause. The majority (n=48) experienced natural as opposed to induced menopause (n=10). Of the total cohort, 23 PM did not use any kind of hormone therapy. The experimental procedures were performed in accordance with the Declaration of Helsinki and were approved by the University of Trás-os-Montes and Alto Douro.

Anthropometry and Body Composition

Height was determined by the stadiometer SECA 220 (Seca Corporation, Hamburg, Germany), and weight (W), fat mass, visceral fat area, fat-free mass as well as skeletal muscle mass (SM) were evaluated by an octopolar bioimpedance InBody 720 (Biospace Co. Ltd., Seoul, Korea), complying with the preparation standards specified in the literature (V. H. Heyward, 2010). Skeletal muscle mass index was calculated using the formula proposed by Janssen et al (Janssen et al., 2002): SMI= (SM/W) x 100. Measurements were taken in the morning and after an overnight fast, by the same technician, and the data were electronically imported into spreadsheets using the software Lookin’Body 3.0 (Biospace Co. Ltd., Seoul, Korea).
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**Test Procedure**

Participants performed a graded submaximal exercise test on a cycle ergometer (Ergomedic Monark 839E, São Paulo, Brazil) in the University laboratory at a controlled temperature of 22°C, at least 3 h after their last meal. All participants were instructed to wear light-weight comfortable clothing on the test day, and to refrain from strenuous exercise, smoking and consumption of caffeine and alcohol during the 12 hours prior to the test (V. H. Heyward, 2010). Before the test, participants were familiarized with the Borg (Borg, 1982) analogue scale and a warm up was allowed on the cycle ergometer to gain understanding of the gearing system. Saddle height was adjusted to allow an almost straight (5°) knee position in the bottom stroke with the ankle in a neutral position, and pedal rate was maintained at 50 revolutions per minute (rpm). The test began at a power output of 0 W and the workload was increased by 25 W every 2 min, up until 85% of the maximal HR (ACSM, 2010). The test was interrupted when the predicted HR was reached, the participant could not maintain the required rpm, oxygen uptake remained stable or decreased with an increase in workload, the respiratory quotient was >1.1, or upon the appearance of physical symptoms (e.g., dizziness, cyanosis or pallor). Perceived exertion was recorded every 2 min and blood pressure was measured prior to the test and immediately afterwards.

During the exercise protocol, respiratory gas-exchange variables (oxygen uptake, carbon dioxide, minute ventilation and respiratory exchange ratio) were continuously measured using a portable gas analyzer (COSMED® K4b², Rome, Italy) and HR was continuously monitored with an incorporated Wireless Double Electrode transmitter band (T61 Polar®, Kempele, Finland). Breath-by-breath and beat-by-beat data were averaged in order to provide a data point for each 20 s period.

Prior to each test, the oxygen and carbon dioxide analysis systems were calibrated using ambient air and a gas of known O₂ and CO₂ concentrations according to the manufacturer’s instructions, while the turbine flow meter was calibrated using a 3-L syringe (COSMED * K4b², Rome, Italy).

**Physiological Measurements and Assessments**

The VO₂max was predicted using a linear regression of the mean HR and VO₂ values of the last minute of each stage. The subject’s first (VT₁) and second (VT₂) ventilatory thresholds were determined by two criteria: time course curves of minute ventilation (Vₑ) and time course curves of ventilatory equivalents of O₂ and CO₂ (Vₑ/VO₂ and Vₑ/VCO₂ respectively) (Blain et al., 2005). The VT₁ corresponded to the last point before the first systematic nonlinear increase in Vₑ and Vₑ/VO₂ curves without a corresponding increase in Vₑ/VCO₂. The VT₂ corresponded to the last point before the second systematic nonlinear increase in Vₑ and Vₑ/VO₂ with a concomitant non-linear increase in Vₑ/VCO₂. Based on the above criteria, VT’s were assessed independently by two experienced individuals who then compared their results and reached a consensus. A total of 4 tests were discarded due to a lack of agreement.

The recent guidelines for exercise intensity prescription of 40% and 84% HRR were used for comparison with HRR at individual VT’s (ACSM, 2010; Garber et al., 2011). Exercise intensity ranges were determined
according to the Karvonen method (Karvonen & Vuorimaa, 1988) and \( HR_{\text{max}} \) was determined by the formula proposed by Gellish et al. \[ HR_{\text{max}} = 206.9 - (0.67 \times \text{age}) \] (Gellish et al., 2007).

Measures of central tendency and distribution were examined to describe the results. The \( VO_{\text{2max}} \) values were used to classify the participants into two different groups by performing a K-means clustering analysis (the cut-off value was 31 mL.kg\(^{-1}\).min\(^{-1}\)). A paired t-test was used to compare the HRR at respective ventilatory thresholds (VT\(_1\) and VT\(_2\)) with cardiorespiratory exercise intensity guidelines of 40% and 84% HRR. Afterwards, Bland-Altman plots were performed to assess the agreement between methods (Hanneman, 2008). All data met the assumptions of each statistical test, and a 5% statistical significance was established.

Statistical analyses were conducted using the Statistical Package for the Social Sciences program (version 17.0; SPSS Inc., Chicago, IL) and the Bland-Altman plots were performed with the MedCalc software program (version 12.0; MedCalc, Mariakerke, Belgium).

Results

The general and physiological characteristics of the participants are presented in Table 1. All women exhibited a normal muscular condition (Janssen et al., 2002) and the predicted \( VO_{\text{2max}} \) values ranged between 21.09 and 42.00 mL.kg\(^{-1}\).min\(^{-1}\) with a mean value of 29.70 ± 4.79 mL.kg\(^{-1}\).min\(^{-1}\). The group’s cut-off value was 31 mL.kg\(^{-1}\).min\(^{-1}\). The group with lower \( VO_{\text{2max}} \) levels presented a mean value of 26.69 ± 2.44 mL.kg\(^{-1}\).min\(^{-1}\), while the group with higher \( VO_{\text{2max}} \) presented a mean value of 35.00 ± 2.89 mL.kg\(^{-1}\).min\(^{-1}\).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total cohort (n=58)</th>
<th>Lower ( VO_{\text{2max}} ) (n=37)</th>
<th>Higher ( VO_{\text{2max}} ) (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.21 ± 4.49</td>
<td>60.52 ± 4.39</td>
<td>59.66 ± 4.71</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.09 ± 4.92</td>
<td>157.26 ± 5.45</td>
<td>156.79 ± 3.91</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.26 ± 8.99*</td>
<td>68.00 ± 8.92</td>
<td>63.21 ± 8.46</td>
</tr>
<tr>
<td>Fat Mass (%)</td>
<td>34.93 ± 6.34**</td>
<td>36.62 ± 5.64</td>
<td>31.94 ± 6.54</td>
</tr>
<tr>
<td>Visceral Fat Area (cm(^2))</td>
<td>125.99 ± 22.33*</td>
<td>131.43 ± 20.15</td>
<td>116.41 ± 23.22</td>
</tr>
<tr>
<td>Fat-Free Mass (kg)</td>
<td>42.76 ± 4.53</td>
<td>42.83 ± 4.80</td>
<td>42.65 ± 4.11</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>23.36 ± 2.70</td>
<td>23.39 ± 2.86</td>
<td>23.31 ± 2.45</td>
</tr>
<tr>
<td>Skeletal Muscle Mass Index (%)</td>
<td>35.52 ± 3.55**</td>
<td>34.58 ± 3.16</td>
<td>37.18 ± 3.65</td>
</tr>
<tr>
<td>( VO_{\text{2max}} ) (mL.kg(^{-1}).min(^{-1}))</td>
<td>29.70 ± 4.79**</td>
<td>26.69 ± 2.44</td>
<td>35.00 ± 2.89</td>
</tr>
<tr>
<td>( VO_{2,\text{VT}1} ) (%)</td>
<td>51.84 ± 10.70**</td>
<td>54.96 ± 10.83</td>
<td>46.35 ± 8.08</td>
</tr>
<tr>
<td>( VO_{2,\text{VT}2} ) (%)</td>
<td>73.01 ± 9.84**</td>
<td>75.99 ± 9.19</td>
<td>68.17 ± 9.08</td>
</tr>
<tr>
<td>HRR (_{\text{VT}1} ) (%)</td>
<td>39.01 ± 10.71</td>
<td>39.70 ± 11.37</td>
<td>37.80 ± 9.58</td>
</tr>
<tr>
<td>HRR (_{\text{VT}2} ) (%)</td>
<td>68.83 ± 12.55</td>
<td>69.54 ± 13.66</td>
<td>67.68 ± 10.73</td>
</tr>
</tbody>
</table>

\( VO_{\text{2max}} \), maximal oxygen uptake; \( VO_{2} \), oxygen uptake; HRR, heart rate reserve; VT\(_1\), first ventilatory threshold; VT\(_2\), second ventilatory threshold; SD, standard deviation; * P ≤ 0.05; ** P ≤ 0.01

A paired sample t-test demonstrated that women’s HRR values at VT\(_1\) are similar to HRR percentage values of 40% in both \( VO_{\text{2max}} \) groups (-0.30% in PM with lower \( VO_{\text{2max}} \) and -2.20% in PM with higher \( VO_{\text{2max}} \), respectively). At VT\(_2\), even though negative, both \( VO_{\text{2max}} \) groups exhibited differences (p<0.01) for the predicted 84%HRR intensity (-14.46% in lower \( VO_{\text{2max}} \) group and -16.32% for higher \( VO_{\text{2max}} \) group level). The HRR at VT\(_2\) in both \( VO_{\text{2max}} \) groups is lower than the value at 84%HRR.
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### Study 3: Table 2 - Comparison of %HRR mean values at VT1 and VT2 to cardiorespiratory training zone guidelines of 40% and 84% in the two VO\textsubscript{2max} groups. Results from paired samples t-test.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>%HRR Guidelines</th>
<th>HRR at VT</th>
<th>p</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower VO\textsubscript{2max}</td>
<td>37</td>
<td>40%</td>
<td>39.70% ± 11.36</td>
<td>0.873</td>
<td>0.04</td>
</tr>
<tr>
<td>Higher VO\textsubscript{2max}</td>
<td>21</td>
<td>40%</td>
<td>39.80% ± 9.58</td>
<td>0.305</td>
<td>0.03</td>
</tr>
<tr>
<td>Lower VO\textsubscript{2max}</td>
<td>34</td>
<td>84%</td>
<td>68.54% ± 13.66</td>
<td>0.000*</td>
<td>1.52</td>
</tr>
<tr>
<td>Higher VO\textsubscript{2max}</td>
<td>21</td>
<td>84%</td>
<td>67.68% ± 10.74</td>
<td>0.000*</td>
<td>2.20</td>
</tr>
</tbody>
</table>

Lower VO\textsubscript{2max}, 21.09 – 30.82 mL.kg\textsuperscript{-1}.min\textsuperscript{-1}; Higher VO\textsubscript{2max}, 31.19 – 42.00 mL.kg\textsuperscript{-1}.min\textsuperscript{-1}; VO\textsubscript{2max}, maximal oxygen uptake; HRR, heart rate reserve; VT, ventilatory threshold; * P ≤ 0.01; ES, effect size.

The Bland-Altman analysis of 40%HRR versus VT\textsubscript{1} showed a mean difference of -0.3%HRR (95% CI: -4.09 to 3.49) and -2.20%HRR (95% CI: -6.57 to 2.16) in lower and higher VO\textsubscript{2max} groups, respectively (see Figure 1). Also in lower and higher VO\textsubscript{2max} groups’ plots, the analysis of 84%HRR versus VT\textsubscript{2} showed a mean difference of -14.5%HRR (95% CI: -19.23 to -9.69) and -16.3%HRR (95% CI: -21.20 to -11.43), respectively.

In both groups, the obvious patterns in the differences around the bias showed that 40%HRR seemed to correctly estimate the value obtained at VT\textsubscript{1}, and that an upper limit of 84% overestimates the HRR percentage value for VT\textsubscript{2}, with the majority of participants below that intensity and below the dotted line of zero.

### Study 3: Figure 1 - Bland–Altman plots showing differences between first (A1; B1) and second (A2; B2) ventilatory thresholds (VT\textsubscript{1} and VT\textsubscript{2}) and the cardiorespiratory training intensities of 40% and 84% HRR, in the two groups of VO\textsubscript{2max}. The upper and lower dotted lines represent the upper and lower 95% limits of agreement (mean differences ± 1.96SDs of the differences), respectively. Lower VO\textsubscript{2max} range: 21.09 – 30.82 mL.kg\textsuperscript{-1}.min\textsuperscript{-1} and Higher VO\textsubscript{2max} range: 31.19 – 42.00 mL.kg\textsuperscript{-1}.min\textsuperscript{-1}. 

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Discussion

The purpose of this study was to examine the heart rate reserve (HRR) at first and second ventilatory thresholds (VT’s) in postmenopausal women and compare it with optimal intensity range recommended by the ACSM (40%-84%HRR). An additional aim was to evaluate whether a higher level of VO$_{2\text{max}}$ corresponded to higher HRR at VT’s. The main findings of this study confirmed the hypothesis that, regardless of the aerobic power level, the lower limit of VT’s matched to 40%HRR. Also, the upper limit of 84%HRR is too high in relation to the value achieved at the second ventilatory threshold. This suggests that the cardiorespiratory target zone for this population should be lower and narrower (40%-70%HRR) than that recommended for the general population. In fact, this range might be more accurate in order to maintain or improve the aerobic metabolism of PM.

Women experience significant changes in endocrine function during aging. Prescribing accurate exercise intensities is a key factor to develop CRF and achieving specific metabolic requirements (ACSM, 2010; Garber et al., 2011; V. H. Heyward, 2010) either in normal or in special populations, such as PM. The menopausal transition is a period of strong hormonal instability that marks a chapter of physiological changes associated with diminished fertility, menstrual cycle irregularity and vasomotor symptoms. In the first two years, the most significant changes include a decrease in ovarian reserve levels that is directly related to early intracycle inhibin-B reduction and anti-Mullerian hormone levels (Burger, Hale, Robertson, & Dennerstein, 2007; S. D. Harlow et al., 2012). This decline in inhibin-B causes an increase in follicle-stimulating hormone, which in turn appears to be an important factor in the maintenance of estradiol concentrations (Burger et al., 2007; S. D. Harlow et al., 2012). The stabilization period of high follicle-stimulating hormone levels and low estradiol values, which lasts between three and six years (S. D. Harlow et al., 2012), limits the stimulation of estrogen receptors (ER-α and ER-β) and their role in modulating the effector cells’ immune response and proliferation (Cutolo, Sulli, & Straub, 2012).

Moreover, the loss of estrogen or its receptors contributes to the development of disorders such as osteoporosis, neurodegenerative and cardiovascular diseases, insulin resistance, and several types of cancer and obesity (Deroo & Korach, 2006).

Advancing age, obesity and menopausal transition also appear to largely contribute to sarcopenic obesity because inflammatory cytokines produced by adipose tissue, especially visceral fat, accelerate muscle catabolism and contribute to a vicious cycle that triggers and sustains sarcopenic obesity (Schrager et al., 2007; Vincent et al., 2012). Moreover, the combination of the age-related decrease in growth hormone and insulin-like growth factor-1 seems to be associated with many changes that can lead to loss of morphological, musculoskeletal, cardiorespiratory and metabolic fitness (ACSM, 2010; Asikainen et al., 2004; Copeland, Chu, & Tremblay, 2004). Sedentary women are especially vulnerable. Some earlier studies showed that menopausal status did not affect CRF when age and training levels were accounted for (Wells, Boorman, & Riggs, 1992). However, recent studies have shown that estrogen deficiency can be responsible for peripheral circulation changes and that menopause by itself can cause an impairment of
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cardiorespiratory response during exercise (Mercuro et al., 2006). In addition, an excess of visceral adiposity combined with poor muscular condition is associated with CRF impairment (Aragao et al., 2011). Moreover, the relative VO$_{2\max}$ loss rates for trained or active individuals are similar to those of their sedentary peers, possibly mediated by a baseline effect and/or a marked age-related decline in exercise training volume and intensity (Tanaka & Seals, 2003). Besides, age-associated reductions in endurance exercise performance is up to threefold greater in women compared to men, with the major differences occurring after 60 years of age (Hawkins & Wiswell, 2003; Tanaka & Seals, 2003).

Therefore, adequate exercise programs can help to neutralize the aging and obesity detrimental effects in PM by increasing aerobic power and muscle strength, preserving normal bodyweight and lipid profile, decreasing hypertension and reducing central adiposity (Asikainen et al., 2004; Polidoulis, Beyene, & Cheung, 2012; Vincent et al., 2012).

Defining and monitoring exercise intensities using percentages of HR$_{\max}$ or HRR is commonplace given the impracticality of using of VO$_{2\max}$ proportions in field-based conditions. However, though some studies relate VT’s with the percentages of HR$_{\max}$ (Ahmaidi et al., 1998), the exercise intensities can be underestimated or overestimated when using the %HR$_{\max}$ method (Lounana, Campion, Noakes, & Medelli, 2007). On the other hand, the HRR method is slightly more accurate because it accounts for individual differences on fitness level and training adaptations, through the resting HR (V. H. Heyward, 2010). For these reasons, the %HRR method was selected for this study. Furthermore, participants were matched, according to their maximal aerobic power, into two cluster groups (lower and higher VO$_{2\max}$; cut-off of 31 mL.kg$^{-1}$.min$^{-1}$) for an independent fitness level analysis.

The data obtained in this study suggests that, VO$_{2\max}$ fitness level aside, 40%HRR is an excellent estimate of VT$_1$ and therefore of the lower limit of intensity for this population. This fact can be supported by the latest Position Statement from the ACSM (Garber et al., 2011) and several other studies that cross physical activity with conditions often associated with menopause (e.g., obesity) (ACSM, 2010), sarcopenia (Visvanathan & Chapman, 2010), osteoporosis (ACSM, 2010), metabolic syndrome (ACSM, 2010), dyslipidaemia (ACSM, 2010), hypertension (ACSM, 2010), and diabetes mellitus (ACSM, 2010).

Moreover, it is known that blood lactate concentration and acidosis level increases are related to VE rise during incremental exercise, suggesting that ventilatory response to the exercise is triggered by metabolic changes (Sekir, Özyener, & Gür, 2002). Hence, the use of ventilatory thresholds to define a HR range could guarantee a specific interval of intensity in which the stimulus is appropriate and effective to improve health and fitness but at the same time remains safe and pleasant (Ekkekakis et al., 2011). Accordingly, it is interesting to note that the first ventilator threshold is mainly useful in constituting training programs for less active persons or clinical situations (Vallier, Bigard, Carré, Eclache, & Mercier, 2000) while the second ventilatory threshold is more particularly used to plan training programs for active persons or athletes (Vallier et al., 2000).
Regarding the VT$_2$, study data exposed major differences ($p\leq0.01$) in both groups (-14.46% in the lower VO$_{2\text{max}}$ group and -16.32% for the higher VO$_{2\text{max}}$ group) for the expected intensity of 84%HRR. These results suggest that anaerobic threshold occurs at approximately 70% and 68% of the HRR, for lower and higher VO$_{2\text{max}}$ groups, respectively, and that the HRR 84% upper limit is overestimated by the second ventilatory threshold %HRR value. The different mean values between groups in VT$_2$, with the lower VO$_{2\text{max}}$ participants presenting higher values of %HRR may be due to individual intensity, duration or frequency of training (Ahmaidi et al., 1998), as well as the use of a cycle ergometer for testing (Roels et al., 2005). Though the cycle ergometer is ideal for testing this population (V. H. Heyward, 2010), the smaller muscle mass involved and different hemodynamic responses may have underestimated the VO$_{2\text{max}}$ values (Roels et al., 2005). Furthermore, different exercise testing modes can lead to different VO$_{2\text{max}}$ values and also different lactate and ventilatory thresholds (Roels et al., 2005).

In addition, above the second ventilatory threshold an acute rise in lactate concentration, metabolic acidosis, and an accelerated rate of muscle glycogen depletion usually occurs, leading to increased discomfort and pain during the activity (Ekkekakis et al., 2011; Ekkekakis & Petruzzello, 1999), thus, exertion above this point can result in an inability to sustain proper exercise duration. However, short but very intense (i.e., high intensity intermittent training) exercise training may induce similar improvements in CRF, insulin action and skeletal muscle oxidative capacity (Babraj et al., 2009; Nybo et al., 2010). Also, though these results have proved insightful, their practical application in improving exercise adherence is limited due to reports of nausea and light-headedness experienced during the exercise (Richards et al., 2010). Moreover, higher-intensity exercise increases the risk of orthopedic injury and discourages continued participation in exercise programs.

Since shifts in energy substrate mobilization and utilization occur as exercise intensity increases, and many of the beneficial effects of regular exercise in PM, such as reduced insulin resistance, are directly associated with an increased capacity to oxidize fat, these study results enable one to make an observation on the main role of exercise intensity on the influence of the substrate utilization during exercise. Generally, it has been shown that, from low to moderate intensities of exercise, the absolute rate of fat oxidation progressively increases and then decreases as exercise becomes even more intense (Romijn et al., 1993).

In this sense, determining an accurate upper intensity limit in PM is very important to improve exercise prescription.

Despite knowledge of the cardiorespiratory training effect on aerobic and anaerobic threshold improvements, this study showed that the optimal intensity range for this population should be considered somewhat different from the general guidelines. A level of exercise intensity that strikes the optimal balance between effectiveness and enjoyment or safety should be prescribed. This gives particular significance to this upper limit intensity interval (40%-70%HRR), in opposition to that recommended for the general population (40%-84%HRR).
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Conclusions

The upper limit of 84% overestimates the %HRR value at the second ventilatory threshold, and the 40% of HRR lower limit is strongly related to the first ventilatory threshold, suggesting that the cardiorespiratory target zone for this population should be lower (40%-70%HRR) than that recommended for the general population.
References


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Study 4. Should menopausal characteristics be considered during cardiorespiratory exercise prescription in postmenopausal women?
Should menopausal characteristics be considered during cardiorespiratory exercise prescription in postmenopausal women?


Study 4

Abstract

Objective: Menopausal characteristics (i.e., the nature of menopause, hormone therapy, and time elapsed since menopause) are known to affect women’s health-related quality of life. The purpose of this study was to determine whether menopausal characteristics affect the cardiorespiratory exercise response and which characteristics should be considered for exercise prescription.

Methods: Fifty-eight postmenopausal women (60.21±4.49 yrs of age; 66.26±8.99 kg body weight; 157.09±4.92 cm in height; 29.70±4.79 mL.kg⁻¹.min⁻¹ maximal oxygen uptake) participated in this study. A graded 25 W.min⁻² cycle ergometer exercise protocol was applied to assess aerobic power and ventilatory thresholds. Participants’ heart rates and gas-exchange variables were measured continuously using a COSMED K4b² portable gas analyser system. The first and the second ventilatory thresholds were determined by the time-course curves of ventilation and oxygen and carbon dioxide ventilatory equivalents. Using age as a covariate, an analysis of covariance was performed to assess the effect of menopause characteristics upon the data.

Results: Regardless of the nature of menopause, use of hormone therapy, time elapsed since menopause, and the interaction between these characteristics, the participants presented no differences in maximal oxygen uptake values, neither on submaximal variables often used in evaluations of exercise prescription, such as percent of maximal oxygen uptake, maximal heart rate, and heart rate reserve, nor in respiratory exchange ratio and gas exchange energy expenditure at aerobic and anaerobic ventilatory thresholds.

Conclusions: These data suggest that a personalized cardiorespiratory target zone for this population should be set according to the published literature, and that consideration of the individual menopausal characteristics seems to be unnecessary.

Keywords: Exercise prescription, Menopausal characteristics, Ventilatory thresholds, Postmenopausal women
Introduction

The aging process associated with cultural behaviour changes may contribute to an increased tendency among postmenopausal women to become sedentary and to gain weight. In general, postmenopausal women (PM) experience a progressive reduction in lean body mass and overall CRF (Lynch et al., 2002) as well as an increase in total fat mass and visceral fat (Van Pelt et al., 2002). This combination contributes largely to increased rates of morbidity and mortality (Perez-Lopez et al., 2009).

At the same time, a generally inverse linear dose-response relationship exists between the amount of physical activity and/or exercise and all-cause mortality. The American College of Sports Medicine (ACSM) has suggested that cardiorespiratory and metabolic requirements are best achieved with exercise intensities ranging from moderate to vigorous (ACSM, 2010). This exercise intensity range must assure a minimum desirable stimulus, often define as aerobic threshold (VT₁), but prevent the inability to sustain the proper exercise duration at higher submaximal intensities, often define as anaerobic threshold (VT₂).

Also, energy expenditure and substrate utilization during prolonged submaximal exercise is known to depend upon several factors but mostly on the exercise intensity and duration (ACSM, 2010).

Studies have shown that menopausal characteristics, such as the nature of menopause, the use of hormone therapy (HT), and the time elapsed since menopause (TM), are associated with women’s quality of life (Bhattacharya & Jha, 2010; Hess et al., 2012), physical functioning, (Tom et al., 2012), and additional factors, including hemodynamic response -- e.g., blood pressure and heart rate (HR) -- and maximal oxygen uptake (VO₂max) (Aragao et al., 2011; Green et al., 2002; Mercuro et al., 2007).

For instance, some studies have found that as estrogen and progesterone are beneficial to muscle performance, HT may influence the decline in physical functioning (Maltais et al., 2009; D. R. Taaffe et al., 2005; Toivonen et al., 2013). Estrogen administration in healthy PM may also be associated with improved endothelial function and arterial stiffness, enhancing central and peripheral cardiovascular adaptations (Lieberman et al., 1994; Moreau, Donato, Seals, DeSouza, & Tanaka, 2003). Even so, it remains unclear whether - due to a likely smaller deprivation of endogenous hormones - women who have undergone natural menopause, used HT, or experienced a larger duration of menopause show any differences in the physiological variables (generally used to quantify cardiorespiratory exercise intensity), when compared to their peers (i.e., induced menopause, non-use of HT, and minor TM) who experience more abrupt fluctuations in hormone levels. These physiological variables include percentage of heart rate reserve (%HRR), maximal HR (%HRmax), %VO₂max, % reserve oxygen uptake, perceived exertion, talk test, and energy expenditure (EE), among others (ACSM, 2010; V. H. Heyward, 2010). Unfortunately, only a limited number of studies have addressed the age-controlled effect of menopause on physiological changes associated to exercise. Furthermore, because only a few dependent variables are common to all studies, making comparisons is difficult (Green et al., 2002; Mercuro et al., 2006, 2007).

Therefore, because an accurate exercise intensity prescription is a key factor to preserving physical fitness as well as improving psychological well-being and health practices of PM (Aragao et al., 2014; Asikainen et al., 2004), our purpose was to examine whether the menopausal characteristics (i.e., nature of
menopause, HT use, and TM) can affect the physiological response at both aerobic and anaerobic threshold. Additionally, by examining these variables at both aerobic and anaerobic thresholds while controlling for the age effect, we hope to clarify whether the individual menopausal characteristics should be considered to improve the accuracy of cardiorespiratory exercise dosage for this population.

Methods

Subjects and Experimental Design

Part of the methodology used in this study was previously published by our research group (Aragao, Moreira, Gabriel, & Abrantes, 2013). Fifty-eight postmenopausal Caucasian women aged 48-69 years were recruited from the surrounding community through advertising. Table 1 reports the descriptive analysis of the sample. Prior to inclusion in the study, a physician collected the reproductive and medical history of each woman, and each woman granted her informed, written consent to participate in the study. Participants had neither neuromuscular nor neurophysiological diseases that could alter their participation in exercise or present aggravated symptoms while exercising. Women being treated with medication that could potentially influence the outcome of this study (e.g. β-blockers and antihypertensive drugs) and women experiencing premature (North American Menopause Society, 2010) menopause were excluded from this study. The experimental procedures were performed in accordance with the Declaration of Helsinki and were approved by the University of Trás-os-Montes and Alto Douro.

Study 4: Table 1 - Sample physical and physiological characteristics (n=58).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.21 ± 4.49</td>
<td>48.43 – 69.49</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.26 ± 8.99</td>
<td>44.62 – 89.04</td>
</tr>
<tr>
<td>BMI</td>
<td>26.87 ± 3.59</td>
<td>18.69 – 36.35</td>
</tr>
<tr>
<td>Fat Mass (%)</td>
<td>34.93 ± 6.34</td>
<td>18.41 – 48.64</td>
</tr>
<tr>
<td>Visceral Fat Area (cm²)</td>
<td>125.99 ± 22.33</td>
<td>60.64 – 170.62</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>23.36 ± 2.70</td>
<td>18.08 – 29.85</td>
</tr>
<tr>
<td>Skeletal Muscle Mass Index (%)</td>
<td>35.52 ± 3.55</td>
<td>28.08 – 43.95</td>
</tr>
<tr>
<td>VO₂max predicted (ml.kg⁻¹.min⁻¹)</td>
<td>29.99 ± 4.88</td>
<td>20.53 – 44.26</td>
</tr>
</tbody>
</table>

BMI, body mass index; VO₂max, maximal oxygen uptake; SD, standard deviation

Anthropometry and Body Composition

Participant height was determined by the SECA 220 stadiometer (Seca Corporation, Hamburg, Germany), while weight (W), fat mass (FM), visceral fat area (VFA), and skeletal muscle mass (SM) were evaluated by octopolar InBody 720 (Biospace Co. Ltd., Seoul, South Korea) bioimpedance. Both procedures complied with the preparation standards specified in the literature (V. H. Heyward, 2010). Skeletal muscle mass index was calculated using the formula proposed by Janssen et al. (Janssen et al., 2002): SMI = (SM/W) × 100. The cut-off points for obesity and elevated VFA were, respectively, FM ≥ 35% (Lohman & Going, 1998) and VFA ≥ 100 cm² (Williams et al., 1996), while sarcopenia was considered present if SMI ≤ 28% (Janssen
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et al., 2002). Body mass index was determined by BMI = W/height². All measurements were taken by the same technician during the morning following each participant’s overnight fast, and data were electronically imported into spreadsheets using the software Lookin’Body 3.0 (Biospace Co. Ltd., Seoul, South Korea).

Test Procedure

Participants performed a graded submaximal exercise test on an Ergomedic 839E cycle ergometer (Monark, São Paulo, Brazil). All exercise tests were performed 3 hours after participants’ last meals. All participants were instructed to wear comfortable, lightweight clothing on test days and to refrain from strenuous exercise, smoking, and consuming caffeine and alcohol during the 12-hour period prior to the test (V. H. Heyward, 2010).

Before the test, a warm-up period was allowed on the cycle ergometer so participants could gain an understanding of the gearing system. The test began at a power output of 0 W and the workload was increased by 25 W every 2 min, until 85% of the HRmax was reached (Gellish et al., 2007). The test was stopped if any of the following occurred: the predicted HR was reached, the participant could not maintain the required rpm, oxygen uptake remained stable or decreased with an increase in workload, the respiratory exchange ratio (RER) was > 1.1, or if physical symptoms (e.g., dizziness, cyanosis, or pallor) developed.

During the graded submaximal test, oxygen uptake, carbon dioxide, minute ventilation (V̇E), and RER, were continuously measured using a COSMED® K4b² portable gas analyser (COSMED Srl, Rome, Italy). HR was continuously monitored with an incorporated T61 Polar® Wireless Double Electrode transmitter band (Polar, Kempele, Finland). Breath-by-breath and beat-by-beat data were averaged to provide a data point for each 30-second period.

Prior to each test, the gas analyser system was calibrated according to the manufacturer’s instructions (COSMED® K4b², Rome, Italy).

Physiological Measurements and Assessments

Each woman’s aerobic or first ventilatory threshold (VT₁) and anaerobic or second threshold (VT₂) were determined by two criteria: time-course curves of minute ventilation (V̇E) and time-course curves of ventilatory equivalents of O₂ and CO₂ (V̇E/VO₂ and V̇E/VCO₂, respectively) (Blain et al., 2005). The VT₁ corresponded to the last point before the first systematic nonlinear increase in V̇E and V̇E/VO₂ curves without a corresponding increase in V̇E/VCO₂. VT₂ corresponded to the last point before the second systematic nonlinear increase in V̇E and V̇E/VO₂ with a concomitant nonlinear increase in V̇E/VCO₂. Based on the above criteria, VT₁ and VT₂ were assessed independently by two experienced individuals who compared their results and reached a consensus.
VO₂max was predicted using a linear regression of the mean HR and VO₂ values of the last minute of each stage of the submaximal incremental protocol. The HRR was determined according to the Karvonen method (Karvonen & Vuorimaa, 1988) and the HRmax was determined by the formula proposed by Gellish (Gellish et al., 2007): HRmax = 206.9 – (0.67 × age). The HR, HRR, and VO₂ values were expressed as a percentage of their maximal values. Gas exchange EE values during exercise were calculated by the Jeukendrup and Wallis formula (EE = 0.550 × VCO₂ – 4.471 × VO₂) for moderate to high intensity exercise (Jeukendrup & Wallis, 2005).

**Statistical Analysis**

All statistical analyses were performed using the IBM SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, New York, U. S. A.), and 5% significance was established. Measures of central tendency and distribution were examined to describe the results. Normality of distribution was tested using the Shapiro-Wilk test, and data transformations were performed when appropriate. To assess the effects of the menopausal characteristics upon the data, an analysis of covariance (ANCOVA) was performed, using age as a covariate. Bonferroni correction was used to protect against type I errors.

**Results**

Sample mean %FM was 34.93 ± 6.34%, with 55.2% of women exhibiting FM values ≥ 35% (Lohman & Going, 1998). Regarding VFA, only seven PM (12.1%) presented values below 100 cm² (Williams et al., 1996) with a cohort average of 125.99 ± 22.33 cm². All women exhibited a normal muscular condition (Janssen et al., 2002), and the predicted VO₂max values ranged between 20.53 and 44.26 mL.kg⁻¹.min⁻¹ with a mean value of 29.90 ± 4.88 mL.kg⁻¹.min⁻¹. The physiological characteristics of the 58 PM are presented in Table 2.

**Study 4: Table 2 - Physiological variables at aerobic (VT₁) and anaerobic (VT₂) ventilatory thresholds, values are mean, standard deviation and range.**

| Variable | VT₁ (n=58) | | VT₂ (n=55) | |
|----------|------------| |-----------|---|
| VO₂ (mL.min⁻¹) | 1034.95 ± 195.26 | 614.00 – 1507.00 | 1459.18 ± 241.93 | 1024.00 – 1995.00 |
| VCO₂ (mL.min⁻¹) | 941.69 ± 212.01 | 528.00 – 1571.00 | 1522.71 ± 279.64 | 991.00 – 2225.00 |
| RER | 0.91 ± 0.07 | 0.75 – 1.06 | 1.04 ± 0.09 | 0.86 – 1.25 |
| %HRmax | 64.92 ± 7.06 | 46.57 – 80.15 | 81.69 ± 8.18 | 62.55 – 93.75 |
| % VO₂ | 53.01 ± 8.77 | 30.99 – 70.69 | 74.18 ± 9.06 | 55.42 – 90.51 |
| %HRR | 39.96 ± 10.14 | 18.54 – 61.00 | 69.00 ± 12.63 | 39.00 – 89.51 |
| EE (kcal.min⁻¹) | 4.11 ± 0.76 | 2.45 – 5.98 | 5.69 ± 0.95 | 4.03 – 7.78 |

VO₂, oxygen uptake; VCO₂, carbon dioxide output; RER, respiratory exchange ratio; HR, heart rate; HRR, heart rate reserve; EE, energy expenditure
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The overall mean duration of menopause for the participants was 9.46 ± 5.70 years. The majority of participants (82.8%) experienced natural (North American Menopause Society, 2010) as opposed to induced menopause (17.2%), while 60.3% reported the use of HT.

To control for the age effect, Table 3 presents the simple and interactive effects of the three important menopausal characteristics (i.e., nature of menopause, HT use, and TM) on the VO\text{2max} and also on the % VO\text{2max}, % HR\text{max}, HRR, RER, and EE at VT\textsubscript{1} (aerobic) and VT\textsubscript{2} (anaerobic). No differences were detected in the physiological variables within the three menopausal characteristic groups, nor did the interaction of the characteristics seem to affect the studied variables.

**Study 4: Table 3** - Isolated and interactive effect of the menopause characteristics in the variation of the physiological parameters – controlling for age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
<th>Nature of Menopause</th>
<th>Hormone Therapy</th>
<th>Time of Menopause</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Natural</td>
<td>Induced</td>
<td>Non-users</td>
<td>Users</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=48)</td>
<td>(n=10)</td>
<td>(n=23)</td>
<td>(n=35)</td>
</tr>
<tr>
<td>VO\text{2max} (mL.kg\textsuperscript{-1}.min\textsuperscript{-1})</td>
<td>0.631</td>
<td>30.29 ± 0.88</td>
<td>29.38 ± 2.20</td>
<td>0.709</td>
<td>29.56 ± 1.74</td>
</tr>
<tr>
<td>% VO\text{2max} at VT\textsubscript{1}</td>
<td>0.199</td>
<td>52.33 ± 1.53</td>
<td>56.45 ± 3.82</td>
<td>0.335</td>
<td>53.16 ± 3.01</td>
</tr>
<tr>
<td>% VO\text{2max} at VT\textsubscript{2}</td>
<td>0.395</td>
<td>73.46 ± 1.54</td>
<td>75.82 ± 3.84</td>
<td>0.582</td>
<td>75.00 ± 3.03</td>
</tr>
<tr>
<td>%HR\text{max} at VT\textsubscript{1}</td>
<td>0.440</td>
<td>64.30 ± 1.23</td>
<td>70.09 ± 3.07</td>
<td>0.096</td>
<td>66.86 ± 2.43</td>
</tr>
<tr>
<td>%HR\text{max} at VT\textsubscript{2}</td>
<td>0.275</td>
<td>80.99 ± 1.36</td>
<td>85.94 ± 3.39</td>
<td>0.195</td>
<td>84.59 ± 2.67</td>
</tr>
<tr>
<td>%HRR at VT\textsubscript{1}</td>
<td>0.539</td>
<td>39.35 ± 1.76</td>
<td>45.43 ± 4.42</td>
<td>0.221</td>
<td>41.29 ± 3.49</td>
</tr>
<tr>
<td>%HRR at VT\textsubscript{2}</td>
<td>0.314</td>
<td>67.94 ± 2.04</td>
<td>74.57 ± 5.07</td>
<td>0.245</td>
<td>73.11 ± 4.00</td>
</tr>
<tr>
<td>RER at VT\textsubscript{1}</td>
<td>0.647</td>
<td>0.90 ± 0.01</td>
<td>0.92 ± 0.03</td>
<td>0.457</td>
<td>0.91 ± 0.02</td>
</tr>
<tr>
<td>RER at VT\textsubscript{2}</td>
<td>0.562</td>
<td>1.03 ± 0.02</td>
<td>1.05 ± 0.04</td>
<td>0.691</td>
<td>1.05 ± 0.03</td>
</tr>
<tr>
<td>EE at VT\textsubscript{1} (kcal.min\textsuperscript{-1})</td>
<td>0.606</td>
<td>4.12 ± 0.13</td>
<td>4.34 ± 0.33</td>
<td>0.546</td>
<td>4.31 ± 0.26</td>
</tr>
<tr>
<td>EE at VT\textsubscript{2} (kcal.min\textsuperscript{-1})</td>
<td>0.828</td>
<td>5.68 ± 0.16</td>
<td>5.85 ± 0.41</td>
<td>0.071</td>
<td>5.99 ± 0.32</td>
</tr>
</tbody>
</table>

VO\text{2max}, maximal oxygen uptake; HR\text{max}, maximal heart rate; HRR, heart rate reserve; RER, respiratory exchange ratio; EE, energy expenditure; * Quadratic transformation for improving asymmetry of the distribution; ^ Normalization of distribution through a quadratic transformation.

**Discussion**

The purpose of this study was to examine whether menopausal characteristics (i.e., nature of menopause, HT use, and TM) should be considered when prescribing cardiorespiratory exercise to PM. The main findings confirmed that, regardless of the presence of and interaction between any of these characteristics, PM present no differences in the predicted VO\text{2max} values neither on the %VO\text{2max}, %HR\text{max}, HRR, RER, and EE at aerobic and anaerobic VTs.

The health benefits of engaging a physically active lifestyle have been well-established, and regular exercise is generally indicated as a key element in the management of a large number of medical disorders and conditions often associated with menopause (e.g., obesity, sarcopenia, osteoporosis, metabolic syndrome, dyslipidaemia, hypertension, and diabetes mellitus) (ACSM, 2010; Asikainen et al., 2004; V. H. Heyward, 2010). In some cases, exercise may be as effective as medical treatment, enhance the effect of medical treatment -- or in special situations be even more effective (ACSM, 2010; Garber et al., 2011).
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Though some exercise is generally preferable to physical inactivity, a desirable minimum and maximum amount (dose) of exercise and intensity is associated with optimal exercise energy expenditure and fat metabolism (ACSM, 2010). The dosage of exercise intensity is, therefore, a key factor for exercise adherence, with higher intensities being associated with reduced pleasure or increased displeasure during the activities (Ekekakis et al., 2011).

Several physiological variables are available to estimate relative exercise intensity during cardiorespiratory exercise. To study the effects of menopausal characteristics, we selected some of the most preferred and commonly used variables (see Table 3); and, because exercise intensity is usually defined as a range (i.e. lower and upper limits), each variable was studied at both aerobic and anaerobic thresholds.

Natural menopause (as the use of HT) is usually associated with less abrupt estrogen reductions when compared to induced menopause (and non-use of HT). Also, induced menopause and a younger age of menopausal onset are generally thought to promote worse physical functioning during older adulthood (Tom et al., 2012). Furthermore, the available evidence regarding TM reveals that the most significant menopausal changes caused by sexual hormone exhaustion occur during the first two years and that the stabilization period can last between three and six years after menopausal onset (S. D. Harlow et al., 2012) - thereby limiting the concentrations of estrogen and triggering an altered production of adipokines by the adipose tissue (especially intra-abdominal) with cardiovascular reflexes (Lee et al., 2013). In this manner menopause characteristics’ might subsequently affect the cardiovascular systems of women, since the mechanisms by which estrogen (and nitric oxide) withdrawal may influence, include an decrease in cardiac output, vasoconstriction and an impairment in peripheral vascular reactivity (Lieberman et al., 1994; Mercuro et al., 2006; Tagawa, Tagawa, & Shimokawa, 1995). Also, we point out the reduced sensitivity of tissues to insulin, the proliferation of smooth muscle cells for endothelium, and fibrinolysis (Deroo & Korach, 2006; Lee et al., 2013; Perez-Lopez et al., 2009).

Hence, we were somewhat surprised by the lack of significant differences ($p < 0.05$), as the studied variables data revealed a similar cardiovascular, respiratory and metabolic response within the groups. Additionally, to note that $\text{VO}_{2\text{max}}$ values were very similar between the menopausal characteristics’ groups. Nonetheless, our data (see Table 3) suggests a pattern regarding the nature of menopause and TM. Women with a shorter TM, as well as PM that underwent induced menopause, exhibited a pattern of slightly greater and better values regarding the physiological variables.

Leading to an incorrect assessment of the minimum and maximum exercise dose and intensity that could compromise effectiveness (e.g. fat metabolism due to optimal substrate utilization, improvements in fitness and/or health), safety (e.g. orthopedic injury and cardiovascular incidence) and its impact on adherence (since pleasure is reduced mainly above the ventilatory or lactate threshold or the onset of blood lactate accumulation).

As a result, though menopause may represent an important cause in impairment of exercise capacity (Aragao et al., 2011; Mercuro et al., 2006), our data suggests that the nature of menopause, use of HT, or TM has no significant effect on a woman’s $\text{VO}_{2\text{max}}$, $\%\text{VO}_{2\text{max}}$, $\%\text{HR}_{\text{max}}$, $\%\text{HRR}$, RER, and EE. Our findings
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suggest that the cardiorespiratory target zone for this population should be personalized according to the literature (ACSM, 2010; Aragao et al., 2014; Aragao et al., 2013; Garber et al., 2011) but that individual menopausal characteristics need not be taken into special account. Moreover, because recent findings (Abildgaard et al., 2013) suggest that reduced whole body fat oxidation after menopause is associated with reduced lower lean body mass values, a variety of exercise modes triggering different impact stresses on the body and especially in the lower limbs (e.g., bench-step, aerobic dance, and walking) would be ideal. Plus, as regular physical activity and EE decreases with age and menopausal transition (Duval et al., 2013), an effective behavioral weight-loss program should include reductions in energy intake.

Finally, one must consider that the relationships among exercise EE, HRR, %HR max, and %VO2 max can vary considerably depending on exercise test protocol, exercise mode, exercise intensity, resting HR, fitness level, age, and body composition, among other factors. Therefore, though the cycle ergometer is ideal for testing this population (V. H. Heyward, 2010), the specific muscle mass required and different hemodynamic responses may lead to underestimated VO2 max and EE values (Roels et al., 2005). Furthermore, different exercise testing and training modes can lead to different VO2 max and VO2 submaximal values, different lactate and VTs (Roels et al., 2005), and different influences of the similar VO2 max values within the groups. Moreover, the between-groups similarities in VO2 max values may mask or hide potential effects of the menopausal characteristics. Future further studies are needed to support these results.

Conclusion

In conclusion, regardless the nature of menopause, use of HT, TM, and the interaction between these characteristics, our study’s PM participants present no differences in the predicted VO2 max values neither on the %VO2, %HR max, %HRR, RER, and EE at aerobic and anaerobic VTs. This suggests that the cardiorespiratory target zone for this population should be personalized according to suggestions in published literature, but that individual menopausal characteristics may not be taken into special account.


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Chapter 4: General Discussion
General Discussion

Assisting the “Shape Up During Menopause” program since its beginning and throughout all its years raised intriguing questions about the postmenopausal period. In order to find some answers or just to help in shed some light into those interrogations, the aim of this investigation was to analyze the interaction of menopausal characteristics with exercise and physical fitness, to evaluate optimal cardiovascular exercise intensities, and to examine the effects of this 12-month multicomponent exercise program on body composition.

Firstly, the salient findings of the present dissertation revealed an impairment of CRF with increasing age and TM, but especially in the presence of total and central adiposity or reduced SMI. Secondly, all the anthropometric and body composition variables along with the BMR were influenced by the exercise program (combining step aerobics, muscle strength, and flexibility/postural control). Furthermore, no interactive effects were found between the exercise and menopausal characteristics, suggesting that exercise alone can promote improvements in postmenopausal women’s body composition. Thirdly, in PM women, aerobic power aside, an upper limit of 84% overrates the %HRR value for the second ventilatory threshold, suggesting that the cardiorespiratory target zone for PM should be lower and narrower (40%-70%HRR) than that recommended for the general population (40% - 84%HRR). Lastly, regardless of the nature of menopause, use of HT, TM, and the interaction between these characteristics, our study’s PM participants present no differences in the predicted VO\textsubscript{2max} values, nor do they on the % VO\textsubscript{2}, % HR\textsubscript{max}, % HRR, RER, and EE at aerobic and anaerobic VTs, suggesting that individual menopausal characteristics may not be taken into special account during cardiorespiratory exercise prescription.

Being part of the team that assessed the physical fitness at baseline in 2006 of the PM participating in the “Shape Up During Menopause” program allowed me to personally observe and also hear these women’s complaints about the deleterious transformations in their bodies and also on CRF. Although, unsurprisingly, effects of postmenopause were present and recognizable, not all women shared the same level of transformations or complaints. So, naturally we started to wonder if there was any connection. Could the body composition and menopause characteristics affect the VO\textsubscript{2max} of PM? However, literature wasn’t clear on this topic.

Nonetheless, two conditions usually associated with postmenopause – sarcopenia and obesity – are known to enhance the risk of functional impairment and physical disability (Janssen, 2010; Zamboni et al., 2008) as to gait and balance deficits (Waters et al., 2010), among others. So with the background of the empiric observations, it was with relatively no surprise that after examination our data suggested that the deterioration of the muscular condition and the increase of adiposity (especially central) could seriously compromise aerobic capacity. Accordingly, non sarcopenic and non-obese women exhibited superior VO\textsubscript{2max} values compared to obese and non-sarcopenic and obese and sarcopenic; additionally, women with a normal visceral fat area and muscular condition presented better VO\textsubscript{2max} values when compared to elevated visceral fat area and non-sarcopenic and elevated visceral fat area and sarcopenic groups. Given...
the well-reported age effect in the aerobic power, we were however surprised that this decrease in VO\(_{2\max}\) revealed a greater association with these muscular condition and fat variables than with age. However, as referenced in the study, the minor association of VO\(_{2\max}\) with age compared to body composition variables could be due to the cohort age distribution (56.7% with 50–59 years).

So we had the part of the answer, but we were missing other, less palpable answers with insufficient and contradictory evidence in literature (Green et al., 2002; McCole et al., 1999; Mercuro et al., 2007; O'Donnell et al., 2009; Statikostas et al., 2008; Szymanski et al., 2005; Uusi-Rasi et al., 2003). Could the menopause characteristics affect the VO\(_{2\max}\) of PM? In our data, TM displayed a significant correlation with VO\(_{2\max}\) and the women with TM >10 years were those who exhibited lower CRF ranks. Though the effect of menopause duration in CRF is not yet considered in literature, the few studies that investigated the effect of the menopausal status in CRF state that this could be related to a worsened arterial vasodilatation response in healthy PM subjects when compared to premenopausal women (Lynch et al., 2002; Mercuro et al., 2006, 2007; Poehlman, 2002). However, since TM was expressed as an ordinal variable (≤10 years; >10 years), the lack of effect of the first variable and the effect of the second should be interpreted with caution.

Given this demonstrated strong effect (regardless of age and time of menopause) of the combination of %FM with %SMI (intimately associated with the menopausal transition) on the variation of the maximum oxygen consumption, a key component for a good health, the need for structured exercise programs designed specifically to attain PM characteristics and needs became even more clear.

So, though we had the most positive feedbacks on the exercise program by the participants every day, as well as some conclusions of positive effects in biomechanical variables (Monteiro, Gabriel, Neves, et al., 2010; Monteiro et al., 2011), we still didn’t know: How much could this 12-month moderate-to-vigorous exercise program (combining aerobic step, flexibility/postural control training, as well as resistance training) improve PM body composition, and especially their total and central adiposity, as well as skeletal muscle mass?

The program “Shape Up During Menopause” was structured and designed specifically by Professor Maria Helena Moreira to attain PM characteristics and needs. Supported by the literature recommendations and findings, it included both aerobic and resistance training, as well as flexibility/postural control. Aerobic training is known to enhance the activity of mitochondrial oxidative enzymes in muscle and protein synthesis (Short et al., 2004), as well as improve lipid and carbohydrate metabolism (V. H. Heyward, 2010), leading to reduction of total and abdominal adiposity (Alberga et al., 2010). Furthermore, the use of a 15 cm (height) step platform allowed participants to generate ground reaction forces beyond 1.5 × body weight (Burr et al., 1983), alternating between 1.6 × body weight in the basic step and 1.99 × body weight in repeaters (Farrington & Dyson, 1995), thereby stimulating osteonal bone formation. Plus, resistance training is known to develop bone mass, fat-free mass, and functional
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performance, and it also reduces the risk of falling (Alberga et al., 2010; V. H. Heyward, 2010; Maltais et al., 2009).

So, with no surprise we confirmed in study 2 what we were able to observe (and inevitably hear from the participants’ feedbacks) almost on a weekly basis during the 12-months intervention. Along with basal metabolic rate, all the anthropometric and body composition variables were influenced by the exercise program. Results showed significant improvements over time in the EXERC body composition, with meaningful positive changes in all variables with the exception of body weight. Still, abdominal obesity has been shown to be a better indicator than body weight for identifying individuals at higher risk of developing chronic disease, which highlights the results of the program (Canoy et al., 2007). The major differences were found in skeletal muscle mass, soft lean mass total, fat-free mass, and skeletal muscle mass index. Also, the differences in visceral fat were higher than those observed for fat mass (kg), suggesting, due to the conclusion in study 1, a positive effect on CRF. These results were particularly meaningful since many studies have suggested that even small variations in the unit of visceral fat can modify the risk of coronary heart disease in older individuals and consequently improve their quality of life (Schousboe et al., 2008; Teede et al., 2010). Plus, central adiposity reduction has significant implications on the muscular and mineral condition of PM.

Interestingly, regarding the regional soft lean mass, the trunk and arms’ subdivisions exhibited the greatest modification. It appears that the benefits from the “Shape Up During Menopause” exercise program, regarding soft lean mass, have been better reflected by the upper body, especially the trunk. Nonetheless, the legs’ soft lean mass also indicated a significant gain after the step aerobics and resistance training program – a feature that can help preserve an independent living at older ages and thus, reduce the risk of morbidity and mortality (Rantanen, 2003). As in a recent study (Sousa, Mendes, Abrantes, & Sampaio, 2011), these results may suggest that the muscles of the lower limbs are elicited more frequently and therefore, have a smaller potential to gain strength at older age and that muscles of the upper limbs are in accelerated muscle atrophy, and their trainability is probably higher.

Since a) TM displayed a significant correlation with \( VO_{2\text{max}} \) (first study); b) the HT literature had such contradictory information effects; and c) the exercise effect considering the nature of menopause was almost nonexistent – an additional purpose in study 2 was to examine the interaction of menopause characteristics with the exercise. However, this time no significant interactive effects were found between exercise and any menopausal characteristics, suggesting an isolated influence of exercise in body composition improvements. These results are in agreement with those that support that exercise alone can promote improvements in body composition (O’Donnell et al., 2009; Szymanski et al., 2005; Teixeira et al., 2003; Uusi-Rasi et al., 2003).

Confirming the vast benefits of this program in body composition and consequently in the health-related fitness of PM, and knowing that in Portugal physical inactivity is highly prevalent in elder but especially in middle-aged women (Baptista et al., 2012) lead us into a new problem/interrogation.
It is becoming increasingly clear that the exercise intensity dose is a key factor for exercise adherence, with higher intensities being associated with reduced pleasure or increased displeasure during the activities; and that pleasure sensation is affected mainly above the anaerobic threshold (ACSM, 2010; Ekkekakis et al., 2011).

Bearing in mind that, as in Portugal, other countries reported low exercise participation rates for menopausal aged women (Baptista et al., 2012; Daley et al., 2007); the question arose, could the recent guidelines that prescribe exercise intensity between 40% – 84% HRR (or even 89% HRR) for adult general population (ACSM, 2010; Nelson et al., 2007) be overrated for PM? Also, another concern was the fact that incorrect assessment of the minimum and maximum exercise dose and intensity could compromise effectiveness (e.g., fat metabolism due to optimal substrate utilization, improvements in fitness and/or health) and safety (e.g., orthopedic injury and cardiovascular incidents). Therefore, we aimed to support or improve the “Shape Up During Menopause” intensity guidelines.

Hence, the concept of the study of ventilatory thresholds was to define an HR range that could guarantee a specific interval of exercise intensity in which the stimulus is appropriate and effective to improve health and fitness but at the same time remains safe and pleasant (Ekkekakis et al., 2011). Also, defining and monitoring exercise using the HRR method is slightly more accurate because it accounts for individual differences on fitness level and training variations through the resting HR chronic adaptations (V. H. Heyward, 2010).

The data obtained in this study (study 3) suggests that, $\text{VO}_{2\text{max}}$ fitness level aside, 40%HRR is strongly related to VT1 and therefore to the lower limit of exercise intensity for this population, which is consistent with the latest Position Statement from the ACSM (Garber et al., 2011) and several other studies that cross physical activity with deleterious conditions often associated with menopause. Regarding the VT2, study data exposed major differences in both groups of aerobic power, suggesting that anaerobic threshold occurs at approximately 70% and 68% of the HRR, for lower and higher $\text{VO}_{2\text{max}}$ level groups respectively, and that the HRR 84% upper limit is clearly above the %HRR value at the second ventilatory threshold, suggesting that the cardiorespiratory target zone (in continuous exercise) for this population should be lower and narrower (40%-70%HRR) than that recommended for the general population.

In the PM population, natural menopause (as the use of HT) is usually associated with less abrupt estrogen reductions when compared to induced menopause (and non-use of HT). Also, induced menopause and a younger age of menopausal onset are generally thought to promote worse physical functioning during older adulthood (Tom et al., 2012). In this manner, menopause characteristics might subsequently affect the cardiovascular systems of women, since the mechanisms by which estrogen (and nitric oxide) withdraw may promote a decrease in cardiac output, vasoconstriction, and an impairment in peripheral vascular reactivity (Lieberman et al., 1994; Mercuro et al., 2006; Tagawa et al., 1995).

So, as in the first studies, in preventing some possible effects, was also determined whether menopausal characteristics affect the cardiorespiratory exercise response and should be considered for exercise
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prescription. For that, some of the most preferred (% VO\textsubscript{2max}, % HR\textsubscript{max}, % HRR, RER, and EE) and commonly used physiological variables to estimate submaximal exercise intensity during cardiorespiratory exercise were selected; and, as previously, they were studied at both aerobic and anaerobic thresholds. Data revealed that, regardless of the presence of and interaction between any of these characteristics, PM present no differences in the predicted VO\textsubscript{2max} values, nor did they on the %VO\textsubscript{2max}, %HR\textsubscript{max}, %HRR, RER, and EE at aerobic and anaerobic VTs. Nonetheless, our data exhibits a pattern regarding the nature of menopause and TM. Women with a shorter TM, as well as PM that underwent induced menopause, exhibited a pattern of slightly greater and better values regarding the physiological variables. As a result, though menopause may represent an important cause in impairment of exercise capacity (Mercuro et al., 2006), cardiorespiratory target zone for this population should be personalized according to the literature, but individual menopausal characteristics need not be taken into special account. Nevertheless, future further studies are needed to support these results.

Practical application

A level of exercise intensity that strikes the optimal balance between effectiveness, enjoyment, and safety should be prescribed. Therefore, the results of this study may lead some to endorse that exercise programs with similar doses (as those of described in “Shape Up During Menopause” program) should be offered to women interested in this type of program. As so, and recommended by the latest guidelines of the American College of Sports Medicine (ACSM, 2010; Garber et al., 2011), attending to the risk factors that are normally associated with central obesity (dyslipidemia, hypertension, hyperglycemia), PM should perform aerobic (cardiovascular endurance) exercises that involve large muscle mass groups (ACSM, 2010; V. H. Heyward, 2010), preferentially every day for 30 to 60 minutes at a moderate-to-vigorous intensity (until 59% heart rate reserve in hypertensive patients). This aerobic exercise should be complemented (2–3 d.wk\textsuperscript{-1}) with a strength (enhance of muscle protein synthesis in myofibrils) and resistance training program (increase in the activity of mitochondrial oxidative enzymes) (Short et al., 2004) at moderate-vigorous intensity (i.e., 60%-80% 1-RM, 8 to 12 repetitions) (ACSM, 2010; Nelson et al., 2007; Perez & Garber, 2011; Dennis R Taaffe, 2006).

In addition, regarding postmenopausal women’s body composition, it seems to be unnecessary to make specific adjustments in the exercise prescription due to the individual menopausal characteristics. Furthermore, a multidisciplinary approach should always be considered key in the search for a healthy body and lifestyle.

Overall limitations

Although the majority of the limitations and drawbacks were already referenced before, their recognition is above all a matter of intellectual honesty. As so, listed:

- Absence of sarcopenic PM without obesity or with a normal visceral fat area;
• Only a small number of participants presented normal values of visceral fat area, simultaneously sarcopenia and obesity, or elevated visceral fat area;
• The inbody720 system has been validated in the literature, but it’s not a gold standard method;
• Participants selection bias, since individuals who volunteer may possess different characteristics than the average individual in the target population;
• Fitness tests and test results alone may have served to motivate women of the control group to increase daily physical activity, affecting the body composition of this group;
• Absence of a plan to control PM daily nutrition and physical activity before, during, and after the exercise program;
• Though the cycle ergometer is ideal for testing this population, the specific muscle mass required and different hemodynamic responses may lead to underestimated VO$_{2\text{max}}$ and energy expenditure values.
References


Chapter 5: Overall Conclusions
Overall Conclusions

The main findings of this work emphasize the importance of:

- A cardiorespiratory fitness impairment with the increasing of age and time elapsed since menopause, but especially when related to total and central adiposity or reduced skeletal muscle mass index.
- The interactive effects of body fat-muscular condition with age, basal metabolic rate and time elapsed since menopause, only basal metabolic rate affected the variation of VO$_{2\text{max}}$.
- Central adiposity-muscular condition had a significant effect on the variation of VO$_{2\text{max}}$.
- The Obese and Non-Sarcopenic and the Elevated Visceral Fat Area And Sarcopenic women groups exhibited higher cardiorespiratory fitness values in ages ≤ 57 years and time elapsed since menopause < 10 years.
- Along with basal metabolic rate, all the anthropometric and body composition variables were influenced by the exercise program.
- No significant interactive effects were found between the exercise and menopausal characteristics.
- In postmenopausal women, aerobic power aside, an upper limit of 84% overrates the % heart rate reserve value at the second ventilatory threshold.
- The cardiorespiratory target zone for postmenopausal women should be lower and narrower than that recommended for the general population.
- Regardless the nature of menopause, use of hormone therapy, time elapsed since menopause, and the interaction between these characteristics, no differences were found in the predicted VO$_{2\text{max}}$ values neither on the % VO$_2$, % HR$_{\text{max}}$, % heart rate reserve, respiratory exchange ratio, and energy expenditure at aerobic and anaerobic ventilatory thresholds.
- Cardiorespiratory target zone for this population should be personalized according to suggestions in published literature, but that individual menopausal characteristics may not be taken into special account.
- These findings provide a reference point (40%-70% heart rate reserve) for the prescription of exercise intensity in this population.
- The results of this study may lead to endorse that exercise programs with similar doses (as those presented in the “Shape up during Menopause”) should be offered to women interested in this type of program.
Chapter 6: Bibliography


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