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Associação entre ingestão alimentar de antioxidantes, composição corporal e variáveis metabólicas em uma amostra de mulheres na pós-menopausa

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Trabalho de conclusão de curso de graduação apresentado ao Departamento de Nutrição da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do Grau de Bacharel em Nutrição.

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A Comissão Examinadora, abaixo assinada, aprova o Trabalho de Conclusão de Curso de Graduação elaborado por Laís Lima Ferreira, como requisito parcial para obtenção de Grau de Bacharel em Nutrição.

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RESUMO

Modificações na composição da dieta aliada à prática de atividade física são importantes estratégias de prevenção para as doenças cardiovasculares, principal causa de morte entre as mulheres na pós-menopausa. Dentre os micronutrientes, evidências sugerem que aqueles com ação antioxidante como zinco, vitamina C e vitamina E possam estar associados com proteção às doenças crônicas. Os polifenóis são compostos presentes em frutas, vegetais e alguns cereais, caracterizados como não nutrientes, possuindo também ação antioxidante. Sendo assim, este trabalho tem por objetivo avaliar a associação entre composição corporal, variáveis metabólicas e risco cardiovascular com a ingestão dietética de antioxidantes em uma amostra de mulheres na pós-menopausa sem doença clínica evidente. Foram arroladas 119 mulheres para este estudo. A absorciometria de raios-x de dupla energia (DXA) foi utilizada para avaliar composição corporal, a atividade física habitual por pedômetro e a calculadora de escore de risco cardiovascular de Framingham para avaliação clínica para do risco cardiovascular. A ingestão dos micronutrientes zinco, vitamina C, vitamina E e de polifenóis foi estimada por meio de um questionário de frequência alimentar validado, categorizada posteriormente em tercis. Preencheram os critérios de inclusão 105 participantes com média de idade 55,2 ± 4,9 anos, tempo de menopausa 6,8 ± 1,0 anos e IMC 27,2 ± 4,6 kg/m². Maiores quantidades de zinco na dieta apresentaram associação maior de massa magra apendicular (p= 0,006), menores níveis de pressão arterial sistólica (p= 0,033) e triglicerídeos (p= 0,042), sendo que as participantes que tinham maior número de passos apresentaram também maior consumo de zinco. Quando as participantes foram estratificadas de acordo com os tercis de ingestão de polifenóis, o tercil 1 apresentou o escore de risco cardiovascular de Framingham maior quando comparado ao tercil 2 (p= 0,032), permanecendo significativo após o controle para tempo de menopausa (p= 0,290). No entanto, a composição corporal e outras variáveis clínicas foram semelhantes entre os tercis de ingestão de polifenóis. Não foram observadas diferenças estatisticamente significativas entre os tercis de vitaminas C e E para variáveis de composição corporal e metabolismo. Em conclusão, os resultados deste estudo sugerem que o maior consumo de zinco e polifenóis na dieta está associado com menor risco cardiovascular nesta amostra de mulheres na pós-menopausa, sem doença clínica evidente.

Palavras chave: menopausa, doenças cardiovasculares, dieta, antioxidantes.

ABSTRACT

Diet composition and physical activity are important prevention strategies against cardiovascular diseases, that is considered main cause of death among postmenopausal women. Among micronutrients, evidence suggests that those with antioxidant action such as zinc, vitamin C, vitamin E and polyphenols may be associated with protection against chronic diseases. Polyphenols are compounds characterized as non-nutrient that have antioxidant action, found in the fruits, vegetables and some cereals. Therefore, this study aims to evaluate the association of body composition and metabolic variables with dietary intake of antioxidants in a sample of postmenopausal women with no evident clinical disease. One hundred and nineteen postmenopausal women were enrolled. Body composition was assessed by dual-energy x-ray absorptiometry, habitual physical activity by a digital pedometer and cardiovascular risk from The Framingham General Cardiovascular Risk Score (10-year risk) (FRS), using lipids. Dietary intake was assessed by a validated food frequency questionnaire. Antioxidants intake, vitamin C, E and polyphenols were stratified into tertiles. One hundred and five participants met the inclusion criteria and were enrolled to the study. Mean age was 55.2 ± 4.9 years, time since menopause 6.8 ± 1.0 years, and BMI 27,2 ± 4,6 kg/m². Women in the higher tertile of zinc intake had greater appendicular lean mass (p=0.006), and mean steps a day (p=0.025), lower systolic blood pressure (p=0.033) and lower triglycerides levels (p= 0.042). Women with lower polyphenol intake (tertile 1) had higher Framingham risk score than tertile 2 (p=0.032), even controlling for time since menopause (p= 0.290). However, body composition and the other clinical variables were similar between between the tertiles of zinc, polyphenols, vitamin E and vitamin C intake. In conclusion, the present results suggest that higher zinc and polyphenol intake are associated with lower cardiovascular risk factors in our sample of postmenopausal women with no evident clinical disease.

LISTA DE ABREVIATURAS

AVC – Acidente vascular cerebral

DCV - Doenças cardiovasculares

HDL – Lipoproteína de alta densidade

IMC – índice de massa corporal

LDL – Lipoproteína de baixa densidade (LDL)

VCT – Valor calórico total

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1 INTRODUÇÃO

A menopausa é um processo que se define como a ausência permanente das menstruações, em decorrência da diminuição da função folicular ovariana, ocorrendo por volta dos 42-58 anos, ou remoção cirúrgica dos ovários, que reflete em uma diminuição quase completa da secreção do hormônio ovariano (FERNANDES, 2008). A pós-menopausa recente corresponde aos primeiros 3-4 anos depois do último sangramento menstrual, e a menopausa tardia são os anos posteriores (HARLOW et al. 2012). O período pós-menopáusico traz intensas modificações hormonais, principalmente a diminuição nos níveis de estrogênio (CLARKSON, 2007), porém o impacto clínico dessas alterações hormonais é variável entre diferentes mulheres, etnias e populações, e apresenta influências de fatores socioculturais e psicológicos (OBERMEYER; REHER; SALIBA, 2007). Sabe-se que o risco para doenças cardiovasculares (DCV) é mais elevado em mulheres na pós-menopausa do que entre as mulheres em idade reprodutiva (COYOY; GUERRA-ARAIZA; CAMACHO-ARROYO, 2016).

A menopausa, com consequente hipoestrogenismo, está associada com alterações cardiovasculares pré-clínicas, como a disfunção endotelial (CABRERA-REGO et al., 2017), e o uso de estrogênio exógeno têm sido associado à melhora da função endotelial em mulheres na pós-menopausa, sendo os benefícios mais evidentes em mulheres nos primeiros anos após a menopausa (MERCURO et al., 1999; SHERWOOD et al., 2007; MATURANA; IRIGOYEN; SPRITZER, 2007). Ativação de mecanismos pró-inflamatórios e alterações na atividade fibrinolítica parecem ter um importante papel na patogênese da aterosclerose e DCV (CARR, 2003; PRIPP et al., 2005).

O sedentarismo e a diminuição do gasto energético, associados ao aumento na ingestão alimentar, contribuem para o aumento do peso com a idade. Já as alterações hormonais da menopausa estariam mais relacionadas às modificações na distribuição da massa de gordura (DONATO et al., 2006) e concentrações circulantes de lipídeos aumentadas (MATTHEWS et al., 2009). Um maior depósito de gordura abdominal parece ser influenciado pelo o *status* menopáusico e a idade (MISSO et al., 2005; DONATO et al., 2006; DOUCHI et al., 2007), sendo considerado um fator de risco para as DCV (ASSOCIAÇÃO BRASILEIRA PARA O ESTUDO DA OBESIDADE E DA SÍNDROME METABÓLICA, 2016), principal causa de

morte nas mulheres nesta fase da vida (LLOYD-JONES et al., 2010; OMS, 2011; GHOLIZADEH; DAVIDSON, 2007). Em estudo prévio do nosso grupo de pesquisa, realizado através de uma análise transversal de 97 mulheres na pós-menopausa, foi encontrado que o índice de massa corporal (IMC), hipoestrogenismo, pressão arterial e os níveis de lipoproteínas de baixa densidade (LDL) podem contribuir para o desenvolvimento de DCV subclínica nessa população (MATURANA et al., 2015).

A presença de obesidade abdominal, dislipidemia, hipertensão arterial, hiperglicemia em jejum ou intolerância à glicose agrava ainda mais o risco de DCV imposto pela menopausa. Intervenções não-farmacológicas devem ser orientadas, entre elas, cessação do tabagismo, dieta com baixo teor de sal e rica em fibras e o aumento da atividade física (CREATSAS; CHRISTODOULAKOS; LAMBRINOUDAKI, 2005; FERNANDES, 2008; OMS, 2011).

1.1 Doenças Cardiovasculares nas Mulheres Pós-menopáusicas e o Desenvolvimento de Aterosclerose

Das DCV com pior morbi-mortalidade entre mulheres pós-menopáusicas estão a doença cardíaca isquêmica e o acidente vascular cerebral (AVC) (LLOYD-JONES et al., 2010; OMS, 2011), os quais estão intimamente ligados ao processo aterosclerótico. A aterosclerose é definida como uma disfunção endotelial complexa induzida pela deposição de LDL em concentrações elevadas e modificadas, por radicais livres, estresse por cisalhamento, hipertensão, microorganismos infecciosos, tabagismo ou combinações destes e outros fatores (ROSS, 1999). A disfunção endotelial é caracterizada pela diminuição da síntese de óxido nítrico, oxidação local das lipoproteínas circulantes e sua entrada na parede vascular (DAVIGNON; GANZ, 2004) e, no caso das mulheres na menopausa, a idade e hipoestrogenismo contribuem para tal disfunção (NAGAI, 1999). As espécies reativas de oxigênio levam ao estresse oxidativo em células vasculares e à ativação da sinalização intracelular de moléculas envolvidas na expressão gênica (ROSS, 1999; FUSTER et al. 2005). A regulação positiva das moléculas de adesão celular facilita a aderência dos leucócitos ao endotélio disfuncional e sua posterior transmigração para a parede do vaso (HANSSON, 2005), levando à ruptura da cápsula fibrosa (FUSTER et al. 2005). A doença aterosclerótica crônica é muitas vezes complicada pela conversão em uma fase aguda, caracterizada por um

tromboembolismo que evolui a partir de placas ateroscleróticas ou por oclusão vascular trombótica (FUSTER et al. 2005). Dos fatores de risco modificáveis para o desenvolvimento da aterosclerose temos o excesso de peso, o consumo aumentado de gordura saturada e a baixa ingestão de frutas e vegetais, dislipidemia, sedentarismo, tabagismo e alcoolismo (FERNANDES, 2008).

1.2 Nutrição na Pós-menopausa

Ainda não existem recomendações nutricionais específicas para mulheres na pós-menopausa. As diretrizes para prevenção de DCV em mulheres (MOSCA et al., 2011) recomendam uma dieta rica em frutas e legumes; escolha de grãos integrais e alimentos ricos em fibras; consumo de peixes, especialmente peixes fontes de ômega 3 (duas vezes por semana); limitar a ingestão de gordura saturada entre 5 - 10% do valor calórico total (VCT) e, se possível até no máximo 7%; colesterol <150 mg/dia; álcool para não mais de uma dose por dia, o que equivale a 12g de etanol; e a ingestão de sódio de <1500 mg/dia. O consumo de ácidos graxos trans deve ser o mínimo possível (< 1% do VCT).

Estudos epidemiológicos vêm sendo desenvolvidos a fim de avaliar o padrão alimentar de mulheres na pós-menopausa e sua associação com desenvolvimento de DCV (CREATSAS; CHRISTODOULAKOS; LAMBRINOUDAKI, 2005, LÓPEZ et al., 2008, MATTHEWS et al., 2009, MOSCA et al., 2011, ALVES; SILVA; SPRITZER, 2016). No estudo de Graff et al. (2017) avaliando mulheres em idade reprodutiva, com síndrome de ovários policísticos, o menor consumo de gordura saturada na dieta foi associado a uma melhor função autonômica cardíaca nos domínios de frequência e tempo, na avaliação da variabilidade da frequência cardíaca. Porém, estudos adicionais são necessários com o objetivo de avaliar o consumo alimentar para identificar as intervenções mais eficientes que podem ser abordadas em campanhas de saúde pública para prevenção de DCV em mulheres após a menopausa (LÓPEZ et al., 2008).

Alguns micronutrientes têm sido reconhecidos como importantes antioxidantes, demonstrando ação protetora para DCV, como zinco, vitamina C e vitamina E. Os componentes não nutricionais polifenóis igualmente apresentam ação antioxidante, assim como efeitos positivos contra as DCV (WANG; CHUN; SONG, 2013).

1.2.1 *Zinco e sua ação antioxidante nas doenças cardiovasculares*

O zinco possui a capacidade de retardar processos oxidativos, que são conhecidos por contribuir na atrofia muscular por desuso (POWERS, 2012). Estudos anteriores mostraram uma associação entre zinco, desempenho físico e massa magra apendicular. No entanto, em uma revisão sistemática recente observou-se que o papel do zinco na sarcopenia permanece inconclusivo (VAN DRONKELAAR et al., 2018). Em um estudo com uma população de idosos saudáveis, a suplementação de 45 mg/dia de zinco durante 6 meses, em comparação ao grupo placebo, foi associada a um aumento do poder antioxidante plasmático e a uma diminuição das concentrações plasmáticas de marcadores pró-inflamatórios e de estresse oxidativo (BAO et al., 2010). Já a deficiência de zinco tem demonstrado interação com a inflamação crônica, estando esta última presente em diversas doenças cardiometabolicas, segundo a literatura (CATANIA; BARROS; FERREIRA, 2009; FOSTER; SAMMAN, 2012). Alguns estudos têm demonstrado que menores concentrações da adipocina zinco-α2-glicoproteína (ZAG) (BING et al. 2004), está associada à obesidade (GE; RYAN, 2014; HOSSEINZADEH-ATTAR et al., 2017), devido sua influência na modulação da inflamação e do metabolismo de lipídeos (HIRAI et al., 1998) e glicose (RUSSEL; TISDALE, 2002). Por outro lado, altas doses de zinco podem causar efeitos adversos, incluindo uma desregulação no sistema imune, inibindo funções das células T e aumentando a expressão de citocinas (IBS 2003) e, igualmente, diminuindo a atividade da superóxido dismutase de Cu-Zn (SAMMAN, 1993). Ensaios clínicos randomizados são necessários para definir de forma mais sistemática quais os níveis seguros de suplementação de zinco em populações variadas. Investigações adicionais sobre os mecanismos moleculares também são necessárias para explicar seus efeitos (FOSTER; SAMMAN, 2012). Poucos estudos avaliaram a relação entre o consumo de zinco e o risco cardiovascular em mulheres pós-menopáusicas.

1.2.2 *Polifenóis e sua ação antioxidante nas doenças cardiovasculares*

Os polifenóis são moléculas derivadas de metabólitos secundários das plantas estando geralmente envolvidos na defesa contra a radiação ultravioleta e de patógenos. Os polifenóis podem contribuir para a coloração, amargor e adstringência dos alimentos. É um composto natural, caracterizado como não nutriente, de ação antioxidante presente em frutas, vegetais e alguns cereais. São conhecidos mais de 8.000 compostos fenólicos, que são subdivididos em

classes, sendo as principais: ácidos fenólicos, flavonoides, estilbenos e lignanos (PANDEY; RIZVI, 2009). Dentre seus efeitos conhecidos na saúde está a ação cardioprotetora, atuando como um potente inibidor no processo de oxidação de LDL, além de sua ação anti-plaquetária, antinflamatória, com capacidade de melhorar a função endotelial, aumentar as concentrações circulantes de HDL (HERNÁEZ et al., 2014), além de ser associado à vasodilatação, consequentemente, reduzindo o risco de aterosclerose (PANDEY; RIZVI, 2009). Ainda, existem associações entre o consumo de polifenóis e menores concentrações de colesterol total e LDL-C (NILSSON et al., 2017), glicemia de jejum, hemoglobina glicada, IMC, fator de necrose tumoral alfa (TNF-α) e pressão arterial sistólica (HUANG et al. 2016). No estudo de Medina-Remón et al. (2017) avaliando 1170 homens e mulheres, foi observado que o consumo de polifenóis por meio da dieta mediterrânea teve associação com níveis diminuídos de biomarcadores inflamatórios e uma melhora em alguns fatores de risco cardiovascular, como o colesterol LDL, colesterol HDL e pressão arterial sistólica e diastólica.

A DCV é ainda a principal causa de morte entre as mulheres pós-menopaúsicas, sendo assim, torna-se importante avaliar se o consumo de antioxidantes dietéticos pode trazer benefícios à saúde dessa população.

2 OBJETIVOS

Avaliar a associação entre composição corporal, variáveis metabólicas e risco cardiovascular com a ingestão de micronutrientes antioxidantes e polifenóis em uma amostra de mulheres na pós-menopausa sem doença clínica evidente.

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ANEXO 1 – ARTIGO

Antioxidants and cardiovascular risk factors

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ABSTRACT

Objective: to characterize dietary intake of antioxidants and polyphenols and to assess whether they are associated with body composition, metabolic variables and a cardiovascular risk score in a sample of postmenopausal women with no clinical evidence of disease. Methods: % body fat, and appendicular lean mass (ALM) were assessed by dual-energy x-ray absorptiometry, and habitual physical activity by a digital pedometer. Dietary intake was assessed by a validated food frequency questionnaire. Antioxidants intake, vitamin C, E and polyphenols were stratified into tertiles. Results: one hundred and five postmenopausal women, 55.2 ± 4.9 years, were included. Women consuming the higher tertile of zinc intake had greater ALM (p=0.006), and mean steps a day (p=0.025), lower systolic blood pressure (p=0.033) and lower triglycerides levels (p= 0.042). Women with lower polyphenol intake (tertile 1) had higher FRS than tertile 2 (p=0.032), even controlling for time since menopause (p= 0.290). Body composition and the other clinical variables were similar between between the tertiles of zinc, polyphenols, vitamin E and vitamin C intake. Conclusions: The present results, in a sample of postmenopausal women with no evident clinical disease, higher zinc and polyphenol intake were associated with lower cardiovascular risk factors.

Keywords: post-menopause, antioxidants, cardiovascular risk factors.

INTRODUCTION

Menopausal transition has been associated with higher prevalence of cardiovascular risk factors and subclinical cardiovascular disease (CVD), due to an acceleration of the atherosclerosis process [1-4]. Dietary strategies are useful to maintain health and prevent a variety of disorders, including CVD, which is still the leading cause of death among men and postmenopausal women [5]. Inflammation and oxidative stress play interconnected and mutually reinforcing roles to accelerate atheroma formation and increase risk for arterial disease [6-7].

Evidence indicates that dietary antioxidants intake, such as zinc, vitamin C, vitamin E and polyphenols exert protective effects in preventing CVD [8]. Impaired zinc homeostasis has been associated with a *status* of increased oxidative stress, and linked to several cardiovascular risk factors, including plasma lipoprotein concentrations [9-10]. Also, current research suggests that vitamin C deficiency, although not a frequent condition is associated with higher risk of mortality from CVD and its supplementation may slightly improve endothelial function and lipid profiles in some groups [11]. The cardio-protective effects of vitamin E are mediated through their antioxidant mechanisms and their ability to suppress inflammation [12]. Polyphenols (flavonoids, lignans, stilbenes) are the most diverse group of phytochemicals distributed in vegetables, fruits, olive oil, and wine and exhibit wide range of protective roles such as hypolipidemic, antioxidative, antiproliferative, and anti-inflammatory effects to reduce disease progression [13-15].

Therefore, the aim of this study was to characterize dietary intake of antioxidants, such as zinc, vitamin C, vitamin E, and polyphenols and to assess whether they are associated with body composition, metabolic variables and a cardiovascular risk score in a sample of postmenopausal women with no clinical evidence of disease.

MATERIALS AND METHODS

Participants and design

In this cross-sectional study, participants were invited by advertisement in local newspapers and radio stations to come to the Gynecological Endocrinology Unit at Hospital de Clínicas de Porto Alegre, Brazil, from October 2010 to February 2012. Inclusion criteria were as follows: 1) menopause, defined as last menstrual period at least 1 year before the

beginning of the study plus follicle stimulating hormone (FSH) levels > 35 IU/L; 2) age between 45 and 65 years; and 3) no use of hormone therapy in the past 3 months. Individuals with diabetes or previous diagnosis of heart disease and current smokers were excluded. One hundred and nineteen postmenopausal women fulfilling all the inclusion criteria were consecutively enrolled, and 105 women completed the study protocol. Eleven candidates were excluded (five with diabetes, one with hyperthyroidism, two with untreated hypothyroidism, two with breast cancer, and one who was premenopausal). An additional three participants dropped out because they were unable to commit to the study (no time for blood collection and indirect calorimetry). The local Ethics Committee approved the study protocol, and written informed consent was obtained from every participant. Details of the participants are described elsewhere [16].

Anthropometric measurements, body composition and resting metabolic rate

Body weight, height, and waist circumference, were measured in duplicate, in the standing position. Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest, perpendicular to the long axis of the body [17]. Appendicular lean mass (ALM) (kg) were assessed by DXA (GE Lunar Prodigy, Radiation Corporation, Madison, WI, USA). Appendicular lean mass index (ALMI) is ALM standardized to squared height. Resting metabolic rate (RMR) was obtained by indirect calorimetry (Fitmate®, Cosmed, Rome, Italy).

Dietary assessment

Dietary intake in the previous month was assessed with a validated food frequency questionnaire (FFQ) consisting of 121 items [18]. Nutritional composition was calculated using the Brazilian Table of Food Composition [19]. Vitamin E was assessed using the United States Department of Agriculture (USDA) National Nutrient Database for Standard Reference [20].

Data on the polyphenol content in foods were obtained from the Phenol-Explorer database (www.phenol-explorer.eu) [21]. In the case of regional foods (grape jelly, peas, okra and *chimarrão*, a tea from south Brazil) that are not included in the basis above mentioned other published studies were used [22-25]. Food items of the FFQ containing two or more food components were separated according to their individual ingredients and foods that

contained no polyphenols were excluded from the analysis. The average food consumption was calculated (in g or ml) according to the standard portion sizes used in the FFQ. Individual polyphenol intake from each food was calculated by multiplying the content of each polyphenol by the daily consumption of each food. Total polyphenol intake was calculated as the sum of all individual polyphenol intakes from all food sources encountered according to this process. The total polyphenol was previously adjusted to total energy intake.

Physical activity assessment

Assessment of habitual physical activity was performed with a digital pedometer (BP 148, Tech Line, São Paulo, Brazil). The device was configured individually according to weight (kg) and individual step length. The equipment was used for six consecutive days, providing the weekly average number of steps. Participants were encouraged not to change their physical activity habits during the study [26-27].

Blood pressure and biochemical and hormone tests

Blood pressure was measured by using an automatic blood pressure monitor (Omron HEM742, Rio de Janeiro, Brazil). Two measurements were performed at 10-minute intervals. Blood samples were collected after a 12-hour fast. All samples were obtained between 8 AM and 10 AM. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined by colorimetric enzymatic methods (Bayer 1800 Advia System, Deerfield, IL, USA), with intra- and interassay coefficients of variation (CVs) <3%. Low-density lipoprotein (LDL) cholesterol was determined indirectly using the Friedewald formula: LDL = total cholesterol − HDL − (triglycerides/5). The Framingham General Cardiovascular Risk Score (10-year risk) (FRS) was computed, using lipids, through the online interactive risk score calculator available on the Framingham Heart Study website (www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php) [28].

Statistical analysis

Results are presented as mean ± standard deviation (SD), or median and interquartile range, depending on the Gaussian or non-Gaussian distribution of variables (Shapiro-Wilk

test). Non-Gaussian variables were log-transformed for statistical analysis and reported as back-transformed into their original units. Analysis of variance was used to compare the differences between the tertiles of dietary antioxidants intake. Chi square was calculated for comparisons of dichotomous variables. All analyses were performed using the Statistical Package for the Social Sciences 19.0 (SPSS, Chicago, IL, USA). Data were considered to be significant at $p \leq 0.05$.

RESULTS

The mean age of participants was 55.2 ± 4.9 years, the mean time since menopause was 6.8 ± 1.0 years, and mean BMI was 27.2 ± 4.6 kg/m². Most of participants were white (80%).

Table 1 presents the characteristics of postmenopausal women according to tertiles of zinc intake (<6.6; 6.7 – 8.9 and >9.0mg/day). Tertiles 1 and 2 of zinc intake were lower than the RDA (8 mg/day, for women aged 31-70 years) [29]. Women consuming the higher tertile of zinc intake had greater appendicular lean mass (p=0.006), ALMI(p=0.018), and mean steps a day (p=0.025), and lower systolic blood pressure (p=0.033). Appendicular lean mass and ALMI remained significantly greater in women in the higher tertile of zinc intake even after adjustment for mean daily steps.

Table 2 shows the characteristics of polyphenol intake (<1793.6; 1793.7 – 3008 and >3009 mg/day). Body composition and the other clinical variables were similar between tertiles.

Metabolic variables according to tertiles of antioxidants intake are shown in tables3 and 4.Women consuming higher zinc content presented lower triglycerides levels (p= 0.042), and lower frequency of previous hormone therapy use (p=0.014) (Table 3). When participants were stratified according to tertiles of polyphenols intake, tertile1 had higher FRS than tertile 2(p=0.032), even controlling for time since menopause (p= 0.290).

There were no differences between the tertiles of vitamin E and vitamin C intake on body composition and metabolic variables.

DISCUSSION

In the present study, higher zinc and polyphenol intake were associated with lower cardiovascular risk factors in postmenopausal women, with no clinical evidence of disease. Women with higher zinc intake (>6.7mg/day) had lower systolic blood pressure, and moderate polyphenol intake (1793.7 – 3008 mg/day) was associated with lower FRS. However, there were no differences between vitamin E and vitamin C intake regarding body composition and metabolic variables.

In this study, zinc intake was positively associated with higher muscle mass, expressed by the appendicular lean mass and ALMI in postmenopausal women, even controlling for mean steps a day. Zinc is an essential trace element that plays a key role in several cellular processes, such as counteracting oxidative processes, which are known to contribute to muscle atrophy [30]. However, while previous studies [31-32] has shown an association between zinc, physical performance, and appendicular lean mass, the role of zinc on sarcopenia remains unclear, as reported in a recent systematic review [33]. Besides that, women with higher zinc intake also had higher protein intake (data not shown), since foods sources of zinc and protein are similar. Indeed, in a previous study [34] we found that muscle mass was positively associated with protein intake.

Moreover, in the present study, higher zinc intake was associated with lower systolic blood pressure. Clinical and transational studies have reported an association between zinc and hypertension (HAS) showing that the main links between the development of HAS and zinc deficiency are multiple mechanisms involving oxidative stress damage, apoptosis, and inflammation [35]. Regarding metabolic abnormalities, a negative a negative association was observedbetween the dietary intake of Zinc and the incidence of hyper-triglyceridemia [36]. In a recent systematic review, zinc supplementation has favorable effects on plasma lipid parameters, including significantly reduced triglycerides as well as total cholesterol and LDL cholesterol [37]. In our study,that included apparently healthy postmenopausal women, only triglycerides were associated with higher zinc intake, confirming the notion of a positive impact of this element on the preventionof atherogenesis in postmenopausal women.

Concerning dietary polyphenol content, women with moderate polyphenol intake (1793.7 – 3008 mg/day) had lower cardiovascular risk, as estimated by the FRS. Western populations consume an estimated 1000–2000mg/day polyphenols, mainly from fruits, vegetables and beverages such as tea, coffee, wine and fruit juices [38-39]. A growing

interest on the association of dietary polyphenol intake with major cardiovascular risk factors has been the focus of recent research. Following *in vitro* and *in vivo* studies demonstrating significant effect in regulating inflammatory *status* [40] several epidemiological investigations tested the association between polyphenol intake and hypertension [41] and dyslipidemia [42]. In this sense, flavonoids are the most consumed bioactive polyphenolic, and in a systematic review they were related to lower risk of death from CVD [43]. These inverse associations appeared also with intermediate intakes, suggesting that even relatively small amounts of flavonoid-rich foods may be beneficial [43], which is in agreement with our study. Furthermore, in another recent meta-analysis of prospective cohort studies that assessed the association between dietary flavonoid intake and CVD risk, dietary intakes of six classes of flavonoids significantly decrease the risk of CVD [44]. To the best of our knowledge, this is the first study that evaluated the Framingham cardiovascular risk score associated with polyphenol dietary intake in postmenopausal women.

A strength of the present study is its sample of healthy postmenopausal women, who were mostly non-obese and with no established CVD, allowing us to show the relationship between cardiovascular risk factors in a stage of pre-clinical disease. Limitations include the cross-sectional design, which precludes conclusions regarding the direction of cause and effect. Our semi quantitative food frequency questionnaire is a robust validated in Brazil, food frequency questionnaire [18] assessing 121 items of food consumption during the preceding month was administered by a trained nutritionist, who interviewed each participant for approximately 50 minutes. This procedure probably enhanced the quality and reliability of our dietary data.

CONCLUSION

The present results, in a sample of postmenopausal women with no evident clinical disease, higher zinc and polyphenol intake were associated with lower cardiovascular risk factors. Women with higher zinc intake had lower systolic blood pressure, and moderated polyphenol intake was associated with lower Framingham cardiovascular risk score. Moreover, zinc intake was positively associated with higher appendicular lean mass and ALMI, suggesting that antioxidants dietary intake may have a positive impact in the prevention of atherogenesis and lean mass loss in postmenopausal women.

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TABLE 1. Characteristics of postmenopausal women stratified by tertiles of zinc intake.

	Tertile 1	**Tertile 2**	**Tertile 3**	***P***	***P#***
n	35	35	35		
mg/day	5.2± 1.1[a]	7.8 ± 0.7[b]	11.5 ± 2.5[c]	**<0.001**	
Age, y	56.3 ± 5.2	53.9 ± 4.5	55.3± 4.6	0.098	
Yearsatschool[d]	7.5 ± 4.5	9.6 ± 3.8	8.3 ± 4.3	0.137	
White, n (%)	30 (86)	31 (89)	31 (89)	0.999	
Time since menopause, y[d]	7 (2.9 – 11.2)	6 (2.2 – 10)	5 (3 – 9)	0.755	
Waist circumference, cm	86.5 ± 9.9	84 ± 10.4	89.4 ± 14.8	0.174	
BMI, kg/m²	26.9 ± 4.3	26.5 ± 3.7	28.2 ± 5.5	0.254	
% Body fat	40.7 ± 7.2	39.5 ± 6.7	41.2 ± 7.2	0.581	
Appendicularleanmass, kg[e]	15.5 ± 1.9[a]	16.3 ± 2.3[ab]	17.1 ± 2.1[b]	**0.006**	**<0.001**
ALMI	6.2 ± 0.6[a]	6.5 ± 0.8[ab]	6.7 ± 0.7[b]	**0.018**	**0.005**
SBP, mm Hg	132 (120 - 140)	120 (110 -142)	125 (120 - 144)	**0.033**	
DBP, mm Hg[d]	80 (79,5 – 80,2)	80 (70 - 80)	80 (74 – 81)	0.148	
Meansteps a day	4805 ± 2149.9[a]	6193.9 ± 3287.4[ab]	6657.3 ± 3165.5[b]	**0.025**	
RMR (kcal/d)	1233.3 ± 170.2	1258.8 ± 156.9	1298.4 ± 249.0	0.382	
Previous smoking behavior, %[e]	9 (26)	15 (43)	13 (37)	0.191	

ANOVA, analysis of variance; BMI, body mass index; ALMI, appendicular lean mass index (ALM/h²); SBP, systolic blood pressure; DBP, diastolic blood pressure; RMR, restingmetabolic rate.
Different letters explain difference between tertiles (P <0.05) (ANOVA and Bonferroni's post hoc tests).
[d]Variables analyzed after log transformation.
[e]x2 test.
P#, controlling for mean steps a day (ANCOVA).

TABLE 2. Characteristics of postmenopausal women stratified by tertiles of Polyphenols intake.

	Tertile 1	**Tertile 2**	**Tertile 3**	***P***
n	35	35	35	
mg/day	1301.6 ± 331.2[a]	2424.9 ± 356.9[b]	4113.3 ± 913.5[c]	**<0.001**
Age, y	56.7 ± 5.2	54.8 ± 4.6	54.0 ± 4.5	0.069
Yearsatschool[d]	7.9 ± 4.3	9.4 ± 4.3	8.1 ± 4.1	0.283
White, n (%)	32 (91)	32 (91)	28 (80)	0.287
Time since menopause, y[d]	7.7 ± 5.3	7.0 ± 4.6	5.8 ± 4.3	0.290
Waist circumference, cm	85.4 ± 10.6	83.7 ± 9.6	90.8 ± 14.5	0.059
BMI, kg/m²	26.7 ± 4.0	26.2 ± 3.5	28.6 ± 5.7	0.106
% Body fat	25.8 ± 7.6	26.1 ± 10.0	29.8 ± 10.4	0.167
Appendicularleanmass, kg[e]	16.0 ± 2.2	16.5 ± 1.7	16.4 ± 2.5	0.855
ALMI	6.4 ± 0.7	6.4 ± 0.6	6.6 ± 0.8	0.792
SBP, mm Hg	130.4 ± 20	125.1 ± 15.5	127.7 ± 17.3	0.510
DBP, mm Hg[d]	80.6 ± 10	76.6 ± 9.9	79.0 ± 9.5	0.295
Meansteps a day	5686.8 ± 3233.8	6609.7 ± 2691.7	5359.7 ± 2965.4	0.136
RMR (kcal/d)	1255.6 ± 178.5	1230.1 ± 142.1	1306.2 ± 252.7	0.324
Previous smoking behavior, %[e]	15 (43)	11 (31)	11 (31)	0.481

ANOVA, analysis of variance; BMI, body mass index; ALMI, appendicular lean mass index (ALM/h²); SBP, systolic blood pressure; DBP, diastolic blood pressure; RMR, restingmetabolic rate.
Different letters explain difference between tertiles (P <0.05) (ANOVA and Bonferroni's post hoc tests).
[d]Variables analyzed after log transformation.
[e]x2 test.

TABLE 3. Metabolic and hormonal variables of postmenopausal women stratified by tertiles of zinc intake.

	Zinc			
Variables	**Tertile 1**	**Tertile 2**	**Tertile 3**	***P***
Total cholesterol, mg/dL	222.7 ± 33.2	209.2 ± 32.5	216.3 ± 38.3	0.269
LDL cholesterol, mg/dL	142.7 ± 30.1	133.6 ± 28.3	140.8 ± 31.0	0.412
HDL cholesterol, mg/dL	52.5 ± 10.3	54.8 ± 11.5	53,8 ± 16,1	0.753
Triglycerides, mg/dL[d]	116 (80 – 178)	84 (68 – 131)	88 (67 – 146)	**0.042**
Glucose, mg/dL	92.7 ± 8.2	93.2 ± 9.3ç	94.2 ± 8.7	0.768
Previous Hormone therapy, %	18 (51)	7 (20)	8 (23)	**0.014**
FRS, %	7.3 ± 10.6	4.3 ± 8.2	6.3 ± 9.5	0.079

LDL, low-density lipoprotein; HDL, high-density lipoprotein; FRS: Framingham General Cardiovascular Risk Score. Different letters (a, b) explain difference between tertiles ($P < 0.05$) (ANOVA and Bonferroni's post hoc tests).
[d]Variables analyzed after log transformation.

TABLE 4. Metabolic and hormonal variables of postmenopausal women stratified by tertiles of Polyphenols intake.

Variables	Tertile 1	Tertile 2	Tertile 3	*P*	*P*[e]
Total cholesterol, mg/dL	214.9 ± 28.0	212.0 ± 38.0	221.3 ± 38.3	0.526	
LDL cholesterol, mg/dL	136.4 ± 26.3	136.2 ± 31.0	144.5 ± 31.8	0.423	
HDL cholesterol, mg/dL	52.1 ± 12.01	54.2 ± 13.5	54.8 ± 13.0	0.660	
Triglycerides, mg/dL[d]	136 (112 – 160)	100 (82 – 118)	114 (93 – 135)	0.187	
Glucose, mg/dL	91.8 ±7.7	93.2 ± 9.1	95.2 ±9.1	0.255	
Previous Hormone therapy, %	11 (31)	11 (31)	11 (31)	0.995	
FRS, %	9.4 ± 5.9[a]	6.0 ±3.2[b]	7.6 ± 4.1[ab]	0.032	0.038

LDL, low-density lipoprotein; HDL, high-density lipoprotein; FRS: Framingham General Cardiovascular Risk Score.
Different letters (a, b) explain difference between tertiles (P < 0.05) (ANOVA and Bonferroni's post hoc tests).
[d]Variables analyzed after log transformation.
P[e],controlling for time since menopause (ANCOVA).