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Relationship between moderate-to-vigorous physical activity, abdominal fat and immunometabolic markers in postmenopausal women

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ABSTRACT

Objects: To assess the burden of levels of physical activity, non-esterified fatty acids (NEFA), triacylglycerol and abdominal fat on the immunometabolic profile of postmenopausal women.**Study design:** Forty-nine postmenopausal women [mean age 59.43 (standard deviation 5.61) years] who did not undertake regular physical exercise participated in this study. Body composition was assessed using dual-energy X-ray absorptiometry, and levels of NEFA, tumour necrosis factor- α , adiponectin, insulin and triacylglycerol were assessed using fasting blood samples. The level of physical activity was assessed using an accelerometer (Actigraph GTX3x), and reported as counts/min, time spent undertaking sedentary activities and time spent undertaking moderate-to-vigorous physical activity (MVPA). The following conditions were considered to be risk factors: (i) sedentary lifestyle (<150 min of MVPA per week); (ii) high level (above median) of abdominal fat; and (iii) hypertriacylglycerolaemia (<150 mg/dl of triacylglycerol).**Results:** In comparison with active women, sedentary women had higher levels of body fat (%) ($p = 0.041$) and NEFA ($p = 0.064$). Women with higher levels of abdominal fat had impaired insulin resistance (HOMA-IR) ($p = 0.016$) and spent more time undertaking sedentary activities ($p = 0.043$). Moreover, the women with two risk factors or more had high levels of NEFA and HOMA-IR ($p < 0.05$), as well as an eight-fold higher risk of a high level of NEFA, independent of age ($p < 0.05$). No significant relationship was found between levels of physical activity, abdominal fat, tumour necrosis factor- α and adiponectin ($p > 0.05$).**Conclusion:** Postmenopausal women with a combination of hypertriacylglycerolaemia, a high level of abdominal fat and a sedentary lifestyle are more likely to have metabolic disturbances.

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Introduction

Postmenopausal women are at greater risk of developing diseases such as type 2 diabetes mellitus, atherosclerosis and dyslipidaemia [1–3]. These chronic diseases occur due to remodelling of adipose tissue (derived from a high-fat diet), which is characterized by adipocyte hypertrophy, impairment of vascularization (hypoxia),

infiltration of immune system cells and an increase in pro-inflammatory cytokines [4]. These cytokines act by breaking down adipocytes, which release non-esterified fatty acids (NEFA) into the circulation.

Sustained elevation of the level of NEFA can be a trigger for activation of inflammatory pathways, mainly in adipose tissue, as fatty acids can bind to Toll-like receptor-4 (TLR-4, a receptor on the adipose surface), inducing the production of pro-inflammatory cytokines [e.g. interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β)] [5–7].

Plasma levels of triacylglycerol and NEFA are predominantly derived from food intake and have been linked with many chronic diseases [8–11]. Hypertriacylglycerolaemia can contribute to the

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development of peripheral insulin resistance (e.g. skeletal muscle, adipose and hepatic tissue) as it inhibits insulin action and, consequently, glucose transporter type 4 (GLUT-4) translocation, which is responsible for plasma glucose uptake [12]. This outcome is more likely in postmenopausal women as their muscle cells are more prone to accumulation of fatty-acid derivatives compared with muscle cells in premenopausal women. This could induce postmenopausal women to develop chronic inflammation and insulin resistance [13]. Moreover, hypertriglycerolaemia can predict cardiovascular disease [11].

Physical inactivity has been found to be an independent risk factor for increasing chronic low-grade systemic inflammation and its outcomes [14–20]. In contrast, a healthy lifestyle can be protective for various chronic diseases [21,22]. It has been shown that postmenopausal women who undertake >150 min of moderate-to-vigorous physical activity (MVPA) per week have lower levels of body fat and fasting glucose compared with women who undertake <150 min of MVPA per week [23,24].

Although several studies have investigated the relationship between the level of physical activity and metabolic and inflammatory profiles, they compared subjects who undertook regular physical exercise (regular frequent exercise aiming to improve physical fitness) with sedentary subjects [25–28]. However, most postmenopausal women do not undertake regular physical exercise, and the main contributor to energy expenditure is habitual physical activity (e.g. sweeping, vacuuming, mopping, etc.) [23,29,30]. Accordingly, categorizing the sample by time spent undertaking MVPA is more reliable in clinical practice. Moreover, these studies used subjective methods to estimate the level of physical activity, which is a limitation because this population does not generally have a good understanding of light vs moderate vs vigorous physical activity [31], and the methods used to define categorization of the levels of physical activity [32,33].

Thus, the main objective of this study was to analyse the burden of separate and clustered risk factors (i.e. hypertriglycerolaemia, high level of abdominal fat and <150 min of MVPA per week; assessed objectively using a tri-axial accelerometer) on immunometabolic markers in postmenopausal women.

Materials and methods

Sample

This cross-sectional study was conducted in 2013–2014 in Presidente Prudente, São Paulo state, Brazil. This city, which is the 14th largest city in São Paulo state [34], has approximately 207,000 inhabitants and a human development index of 0.846.

Inclusion criteria for this study were: (i) postmenopausal (i.e. not had a menstrual cycle for at least 1 year); (ii) age >50 years on the date of assessment; (iii) obese (>35% body fat); (iv) not engaged in regular physical exercise for at least 6 months prior to the study; (v) not receiving hormone replacement treatment; (vi) not using drugs such as beta-blockers, statin, etc.; and (vii) signed the written informed consent form for study participation.

All procedures used in this study met the criteria of the Ethics in Human Research according to No. 196/96 of the National Health Council, Brasília, DF. All participants signed an informed consent form approved by the Ethics in Research Committee from the university linked to the project (Protocol: 64/2011).

Data collection

Anthropometry and body composition

For the anthropometric measures, all the participants wore light clothing and were barefoot. Height was measured using a

fixed stadiometer (Sanny, São Bernardo do Campo, São Paulo, Brazil), with accuracy of 0.1 cm. Body weight was measured using a digital scale (Filizola PL 50, Filizola Ltda., Brasil), with accuracy of 0.1 kg.

A dual-energy X-ray absorptiometry (DXA) scanner (Lunar DPX-NT Version 4.7; General Electric Healthcare, Little Chalfont, UK) was used to assess body composition variables. The participants were positioned in a supine position on the table in the DXA machine throughout the examination. The values were expressed as percentage of total body fat and abdominal fat (kg). These results were calculated using the equipment's specific software (EnCORE Version 11.x, Madison, WI, USA).

Practice of habitual physical activity

Habitual physical activity was assessed using an Actigraph tri-axial accelerometer motion sensor (Model GT3X, Actigraph LLC, Pensacola, FL, USA), which recorded movements in the three orthogonal planes (vertical, horizontal anteroposterior and mediolateral).

Accelerometers were attached to an elastic tape and placed on the waist of the subjects, above the hip, at the height of the iliac crest on the right side of the body. The participants were asked to wear the device for 7 days, except when sleeping, bathing and engaging in aquatic activities such as swimming [23].

Specific software (ActiLife5 – Data Analysis Software by Actigraph) was used to process the data obtained. Non-wear time was defined as at least 60 consecutive minutes of zero counts, with allowance for up to 2 min of counts between 0 and 100 [35]. A valid day was defined as ≥ 10 h of monitor wear time, and only participants with at least 5 valid days (including at least one weekend) were included in this analysis [36].

The raw measurement from the accelerometer was determined in counts (arbitrary measure; the greater the number of counts, the higher the level of physical activity). The counts from each sample were summed over a specific period of 60 s, called an 'epoch'; as such, the raw data were expressed in counts/min. The period of 60 s was chosen for this study population because of the low-intensity, long-duration pattern of activity [37].

In an attempt to obtain a biological value and facilitate the interpretation of data provided by the accelerometer (counts), these were translated into minutes of physical activity. The recommendations proposed by Freedson et al. [38] for accelerometers were used to classify the intensity of physical activity. Light physical activity was defined as <1952 counts/min [< 3.00 metabolic equivalents (METs)], moderate physical activity was defined as 1952–5724 counts/min (3.00–5.99 METs), vigorous physical activity was defined as 5725–9498 counts/min (6.00–8.99 METs), and very vigorous physical activity was defined as >9499 counts/min (≥ 9 METs). Freedson et al.'s cut-off point of <100 counts/min was used to categorize an epoch as sedentary.

Accordingly, habitual physical activity was expressed as counts/min, and the percentage of time spent undertaking sedentary activities and MVPA. Women who undertook <150 min of MVPA per week were considered to be sedentary, in accordance with the recommendations of the American College of Sports Medicine [39].

Blood sample, inflammatory and metabolic profile

After a 12-h fast, blood samples were collected by nurses in sterile tubes containing heparin. Levels of triacylglycerol and NEFA were assessed using the colorimetric method with a commercial kit (Labtest, Lagoa Santa, Minas Gerais, Brazil and ZenBio Inc, Research Triangle Park, NC, USA, respectively). Serum levels of insulin, TNF- α and adiponectin were quantified using an enzyme-linked immunosorbent assay (ELISA) from a commercial kit (RayBio Human ELISA Kit, Norcross, GA, USA) in accordance with the manufacturer's instructions. In addition, the homeostatic

Table 1
General characteristics of the sample dichotomized by risk factors (n = 49).

	Sedentary n = 24	Physically active n = 25	p-Value	NAF n = 24	HAF n = 25	p-Value	Normotriacylglycerolaemia n = 35	Hypertriacylglycerolaemia n = 14	p-Value
Age (years)	61.55 (6.23)	55.75 (7.18)	0.016	59.26 (8.06)	59.66 (9.73)	0.689	58.96 (7.45)	60.97 (10.35)	0.658
BMI (kg/cm ²)	29.06 (8.96)	26.90 (5.06)	0.246	25.24 (3.34)	31.56 (4.77)	<0.001	26.90 (7.25)	29.55 (4.02)	0.170
Body fat (%)	46.90 (6.08)	41.50 (8.70)	0.041	40.65 (6.35)	48.30 (6.85)	<0.001	44.30 (10.10)	45.30 (8.55)	0.765
NEFA (µm)	199.17 (63.92)	167.70 (37.37)	0.064	171.63 (35.40)	195.23 (72.77)	0.312	171.63 (43.27)	216.87 (101.28)	0.080
TNF-α (pg/ml)	306.83 (218.40)	314.73 (239.83)	0.920	322.17 (113.93)	261.51 (266.50)	0.230	308.46 (226.97)	293.52 (245.53)	0.833
Insulin (µIU/ml)	9.65 (10.93)	11.09 (11.82)	0.357	8.19 (10.74)	12.95 (7.86)	0.063	9.17 (10.37)	11.56 (9.71)	0.731
HOMA-IR	2.05 (2.86)	2.59 (3.98)	0.503	1.58 (2.57)	3.31 (3.78)	0.016	1.95 (3.30)	3.21 (4.03)	0.283
HOMA-β	115.81 (141.85)	136.79 (138.15)	0.121	134.75 (157.15)	122.00 (154.17)	0.646	137.82 (134.97)	115.43 (159.13)	0.203
Adiponectin (µg/ml)	0.16(0.15)	0.17 (0.23)	0.841	0.16 (0.20)	0.17 (0.16)	0.936	0.17 (0.21)	0.14 (0.09)	0.278
Sedentary behaviour (%)	77.41 (7.62)	71.60 (8.03)	0.001	72.25 (11.07)	76.03 (8.77)	0.043	72.86 (10.99)	74.77 (7.94)	0.084
MVPA (%)	0.83 (0.77)	2.60 (1.65)	<0.001	1.62 (1.24)	1.40 (2.29)	0.509	1.69 (2.03)	1.36 (1.56)	0.259
Counts/min	298.18 (89.90)	432.11 (154.20)	<0.001	399.94 (216.00)	338.21 (140.47)	0.023	356.16 (161.24)	324.17 (179.73)	0.127

NAF, normal abdominal fat; HAF, high abdominal fat; NEFA, non-esterified fatty acids; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; HOMA-IR, homeostatic model assessment-insulin resistance; HOMA-β, homeostatic model assessment-β-cell function; MVPA, moderate-to-vigorous physical activity; BMI, body mass index. Data expressed as median and interquartile range.

model assessment-insulin resistance (HOMA-IR) and homeostatic model assessment β-cell (HOMA-β) were calculated [40].

Criteria to classify the risk factors

A sedentary lifestyle (<150 min of MVPA per week), hypertriacylglycerolaemia (>150 mg/dl) and a high level of abdominal fat (above the median of 2.74 kg) were considered to be risk factors. The median level of abdominal fat was used because there is no validated cut-off level for abdominal fat measured using DXA. Thus, the women were classified into two groups: 'one risk factor or fewer' or 'two risk factors or more'.

Statistical analysis

The Kolmogorov–Smirnov test was used to test the normality of the data set. All data were considered to be non-parametric, and are presented as median, interquartile range and 95% confidence intervals. The Mann–Whitney test was used to compare the data for risk factors separately and in clusters. In addition, the odds ratio of this association was calculated using binary logistic regression to analyse the magnitude of possible associations between risk factors and immunometabolic markers. This regression analysis was adjusted for age. All analyses were performed using Statistical Package for the Social Sciences Version 13.0 (IBM Corp., Armonk, NY, USA). The level of significance was set at 5%.

Results

Of the 77 women evaluated, 60 met the inclusion criteria. Following assessment of physical activity, it was found that 11 participants had not used the accelerometers for at least 4 days during the week and once at the weekend; as such, the final sample consisted of 49 women.

Table 1 presents the results of the comparison between the risk factors separately. Sedentary women had a higher mean percentage of total body fat {46.90% [standard deviation (SD) 6.08] vs 41.50% (SD 8.70); $p = 0.041$ } and a higher mean percentage of time spent undertaking sedentary activities [77.41% (SD 7.62) vs 71.60% (SD 8.03); $p = 0.001$]. Moreover, as expected, sedentary women had lower MVPA and counts/min ($p < 0.001$). Levels of NEFA tended to be higher in sedentary women ($p = 0.064$). The participants were subdivided into two groups using the median value for abdominal fat. Women with an abdominal fat level above the median had higher mean body mass index [31.56 kg/m² (SD 4.77) vs 25.24 kg/m² (SD 3.34); $p < 0.001$], percentage of total body fat [48.30% (SD 6.85) vs 40.65% (SD 6.35); $p < 0.001$], HOMA-IR [3.31 (SD 3.78) vs 1.58 (SD 2.57); $p = 0.016$] and percentage of time spent undertaking sedentary activities [76.03% (SD 8.77) vs 72.25% (SD 11.07); $p = 0.043$], and lower counts/min [338.21 (SD 140.47) vs 399.94 (SD 216.00); $p = 0.023$]. **Table 1** also shows that women with hypertriacylglycerolaemia tended to have a higher level of NEFA and spent more time undertaking sedentary activities ($p < 0.085$).

Table 2 shows the results of women who had one risk factor or fewer compared with women who had two risk factors or more. Women with two risk factors or more had significantly higher mean levels of NEFA [167.70 (SD 27.53) vs 216.87 (SD 98.33), $p = 0.004$] and HOMA-IR (1.81 (SD 2.45) vs 3.57 (SD 5.83), $p = 0.039$).

Table 3 shows the associations between risk factor clusters and levels of NEFA and HOMA-IR. Women with two risk factors or more were eight times more likely to have a high level of NEFA. However, the logistic regression revealed that the association was not significant for HOMA-IR.

Table 2

Comparison between number of risk factors and metabolic and inflammatory markers in postmenopausal women.

Variables	One risk factor or less (n = 29)	Two risk factors or more (n = 20)	p-Value
Age (years)	57.79 (8.49)	61.13 (8.32)	0.173
NEFA (μm)	167.70 (27.53)	216.87 (98.33)	0.004
TNF- α (pg/ml)	314.73 (215.98)	299.85 (271.09)	0.855
IL-6 (pg/ml)	102.86 (12.13)	105.04 (8.47)	0.661
Insulin ($\mu\text{IU/ml}$)	8.19 (10.00)	12.49 (9.62)	0.192
HOMA-IR	1.81 (2.45)	3.57 (5.83)	0.039
HOMA- β	136.79 (151.40)	117.04 (150.12)	0.304
Adiponectin ($\mu\text{g/ml}$)	0.17 (0.27)	0.16 (0.09)	0.714

NEFA, non-esterified fatty acids; TNF- α , tumour necrosis factor- α ; IL-6, interleukin-6; HOMA-IR, homeostatic model assessment-insulin resistance; HOMA- β , homeostatic model assessment- β -cell function.

Data expressed as median and interquartile range.

Comments

This study was unique as it used accelerometers to assess the level of physical activity, and identify the burden of risk factors on the immunometabolic markers. Systemic pro-inflammatory cytokines were not found to be related to the level of physical activity. However, a high level of NEFA may act as a predictor of early chronic systemic inflammation, and can be mediated by the amount of physical activity undertaken. Interestingly, only the women with two risk factors or more had a detrimental metabolic and inflammatory profile. In contrast, having one risk factor or fewer was found to be protective against unhealthy outcomes.

This study demonstrated that TNF- α concentration was not related to the level of physical activity or the risk factor cluster. Knudsen et al. [19] found similar results in a study of acute reduction of steps and overeating. In this study, 14 days of increasing sedentary behaviour did not change the levels of TNF- α and IL-6. However, Dalmás et al. [41] found that inflammation in adipose tissue increased after a reduction in physical activity.

Hypertrophy of adipose tissue, particularly visceral, leads to an increase in its remodelling; under hypoxic conditions, this attracts circulating macrophages due to action of monocyte chemoattractant protein-1 [42]. Macrophages infiltrated into adipose tissue acquire an M1 phenotype, and increase local production of pro-inflammatory cytokines, such as TNF- α and IL-6 [4,22,43], which act by breaking down adipocytes and releasing NEFA into the circulation [4]. Therefore, systemic alterations in NEFA appear to occur before systemic inflammation, and can predict the inflammation of visceral adipose tissue.

Sedentary women had higher levels of body fat and NEFA compared with active women. Corroborating these findings, other studies have found that postmenopausal women who undertook <150 min of MVPA per week had unhealthy metabolic profiles

Table 3

Adjusted odds ratios for number of risk factors in association with metabolic and inflammatory profile.

Variables	Odds ratio (95% CI)	p-Value
NEFA		
One risk factor or fewer	1.00	0.002
Two risk factors or more	8.678 (2.146–35.097)	
HOMA-IR		
One risk factor or fewer	1.00	0.089
Two risk factors or more	2.160 (0.605–7.712)	

95% CI, 95% confidence interval; NEFA, non-esterified fatty acids; HOMA-IR, homeostatic model assessment-insulin resistance.

Binary logistic regression adjusted for age.

[23,24,44]. The present study found that only sedentary women had metabolic disturbances, characterized by high levels of NEFA. In agreement, Franks et al. [45] found that physical activity, measured by heart rate, was negatively correlated with the level of NEFA, and that women in the lower quartile for level of physical activity had higher levels of NEFA.

It is known that a high level of NEFA impairs the sensitivity of peripheral insulin [46]. In various tissues, NEFA act directly or through intermediaries, activating phosphokinase C-theta, which initiates downstream activation of pro-inflammatory proteins [c-JUN NH₂-terminal kinase (JNK) and the inhibitor κ B kinase (IKK)]. JNK and IKK associate with IRS-1, promoting serine-phosphorylation [47], which is responsible for IRS-1 blocking and insulin resistance through interruption of the IR/IRS-1 interaction [48].

Furthermore, in adipocytes, NEFA is responsible for the activation of the Toll-like receptor, especially isoform 4 (TLR-4) [4]. Since TLR-4 becomes activated, it transmits the signal downstream, stimulating a pro-inflammatory pathway via NF- κ B, which binds to its specific promoter region in DNA and transcribes pro-inflammatory cytokine genes, such as IL-6, IL-1 β and TNF- α [5].

A high-fat diet, insufficient physical activity and central adiposity have been reported to be risk factors [11,22,49], and this was also found in the present study. In addition, this study showed that women with two risk factors or more were at eight-fold higher risk of a high level of NEFA. In agreement, Bhagat et al. [50] found that a combination of high intra-abdominal fat, high blood pressure, high level of low-density lipoprotein and hypertriglycerolaemia accounts for 72.97% of the total phenotypic variation in metabolic syndrome. In the present study, the level of NEFA was increased in women presenting with a combination of sedentary behaviour, high level of abdominal fat and hypertriglycerolaemia, independent of age. This result is in accordance with Barton et al. [21], who found that a low level of physical activity can be a trigger for obesity, and can modulate the development of many diseases, such as hypertension, dyslipidaemia and insulin resistance [21].

Undertaking physical activity can protect against several unhealthy outcomes [22], and the findings of the present study support this recommendation in terms of all metabolic and inflammatory outcomes analysed. These results are likely to be due to an active lifestyle, as this generates positive outcomes via different mechanisms, such as the release of immunomodulatory hormones [51]; the reduction of pro-inflammatory cytokine production, due to a decrease in visceral fat mass [52] and TLR-4 expression on macrophages [53]; the suppression of macrophage infiltration of adipose tissue [54]; and the increase in anti-inflammatory myokine production, such as IL-1ra, IL-10 and IL-6 [22].

Despite the significance of these findings, it is important to mention the limitations of this study. As the sample size was small, there is a need for caution in extrapolating the results. The cross-sectional design does not allow for longitudinal considerations, and thus does not allow causal inferences. The strengths of this study should also be highlighted. Perhaps the most notable is the objective measurement of physical activity using a triaxial accelerometer, providing a reliable measure of habitual physical activity and avoiding possible mistakes presented in subjective self-reported physical activity questionnaires. Furthermore, this method enables categorization of the different levels of physical activity, providing opportunities to analyse different patterns.

In summary, these results suggest that postmenopausal women with hypertriglycerolaemia, a high level of abdominal fat and a sedentary lifestyle are more likely to have metabolic disturbances. Therefore, steps must be taken to increase the practice of regular physical activity, coupled with awareness of the need for a low-fat diet.

Conflict of interest

None declared.

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