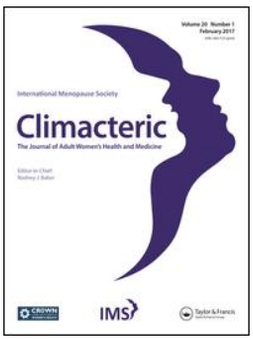

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ORIGINAL ARTICLE

Nordic walking increases circulating VEGF more than traditional walking training in postmenopause

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ABSTRACT

Objectives: Nordic walking (NW) is widely practiced by postmenopausal women. Its effects are peculiar owing to the involvement of more muscle groups than in traditional walking training (WT). Since mechanical load promotes secretion of vascular endothelial growth factor (VEGF) from both skeletal muscle and muscle endothelium, the aim of the study was to compare the effect of NW and WT on VEGF levels.

Method: Thirty postmenopausal women were randomly assigned to NW or WT. Both groups trained 40–50 min/day, three times per week, at a mean intensity of 12 on a 15-category scale of the ratings of perceived exertion. Since VEGF is also released from adipocytes, anthropometric parameters were assessed.

Results: NW increased circulating VEGF more than WT ($p = 0.041$). Furthermore, both study groups exhibited an average decrease in weight ($p = 0.023$), body mass index ($p = 0.024$), hip circumference ($p = 0.001$), and arm fat index, although WT participants had higher values for this index at baseline ($p < 0.001$) and thus exhibited a greater net decrease compared with the NW participants ($p < 0.011$).

Conclusions: These data imply that NW increases the level of circulating VEGF more than does traditional walking when the intensity of training is equivalent.

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Physical exercise; women's health; angiogenesis; ELISA; localized adiposity

Introduction

Physical exercise has been proposed as an alternate mean of improving middle-aged and older women's quality of life[1]. In addition to ameliorating physical fitness, physical exercise has both positive metabolic[2,3] and cardiovascular effects[4,5], decreases systemic low-grade inflammation[6,7], and improves psychological well-being and overall quality of life[1]. In recent years, Nordic walking (NW), a type of physical exercise that utilizes specially designed poles, has increased in popularity world-wide. According to the literature, the correct use of the poles actively engages the upper limbs to propel the body forward during walking[8,9], leading to increased oxygen uptake (VO_2), heart rate, and blood lactate concentration[8] compared with conventional walking training (WT), and its effectiveness has been demonstrated also for postmenopausal health[10].

The involvement of a larger number of muscle groups with NW is an important aspect that can provide further benefits in addition to those already known: during exercise, vasodilation of feed arteries and arterioles in the working muscle tissue is achieved by shear stress (physical interaction of high blood flow with the endothelium)[11]. Shear stress induces the release of circulating humoral factors, including vascular endothelial growth factor (VEGF)[12], which is a key mediator of angiogenesis[13]. Furthermore, VEGF is also released locally[14] and into the bloodstream[15–17] by skeletal muscle in response to both active and passive movement[18,19]. This is possible because two main types of stimuli induce VEGF release from skeletal muscle, namely metabolic (reduced oxygen tension) and mechanical (muscle fiber and endothelium stretch and shear stress)[20]. High-intensity physical exercise promotes increased circulating VEGF levels because it serves as both a metabolic and mechanical stimulus. However, high-intensity physical exercise is not suitable for postmenopausal women, especially those who are physically inactive, which is often the case for these women[21]. On the other hand, VEGF released in response to mechanical stimuli is not influenced by physical exercise intensity[19], and thus it is probable that stimulation of a larger number of muscle groups, such as during NW, would induce a greater release of VEGF. However, no studies have investigated this possibility. Thus, the aim of this study was to evaluate the effect of 13 weeks of NW training or WT, performed at the same intensity, on circulating VEGF level in postmenopausal women. Since VEGF is produced and released also by adipose tissue[22], we evaluated whether VEGF levels after training were accompanied by eventual training-induced body adaptations.

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Materials and methods

Participants

Thirty postmenopausal women (mean age 57.93 ± 3.55 years) were enrolled in the study through advertisements placed in the offices of general physicians in the Pescara area (Italy). The inclusion criteria were: age <65 years; menses had naturally ceased for at least 12 months with plasma estradiol <20 pg/ml; body mass index (BMI) > 18.5 and <35 kg/m^2; no estrogen replacement therapy; no history of orthopedic disease that would impair walking. Further requirements were no participation in either a controlled diet program in the last 2 years or a regular exercise program for 6 months before enrollment. Participants gave written informed consent. The ethics committee of Chieti-Pescara University approved the study.

Procedure

Both the medical examination and body attribute measurements were performed under controlled conditions for temperature (21–23 °C) and humidity (50%). The basal screening (T_0) consisted of collection of medical history data, physical examination, blood sampling, anthropometry, and a maximal stress test. The participants abstained from alcohol consumption and were standardized for fluid intake in the 48 h before the tests. Furthermore, they were not allowed to perform maximal muscle exertion in the 24 h before the screen. Following T_0, the participants were randomly assigned to WT ($n = 15$) or NW ($n = 15$) training programs. The same tests were repeated at the end of the exercise program (T_1).

Blood sampling

Plasma was obtained from 12-h fasting venous blood samples and stored at –80 °C until analysis. Plasma VEGF concentration was determined with an enzyme-linked immunosorbent assay (DRG International Inc., Mountainside, NJ, USA). All samples were processed in duplicate in the same assay. The intra-assay coefficient of variation was <5%, and inter-assay precision was >92%.

Anthropometry and body composition

Body attribute measurements were evaluated under fasting conditions by a specialist in anthropometry in possession of level 2 certification of the International Society for the Advancement of Kinanthropometry. Body weight, height, waist and hip circumferences (WC and HC, respectively), mid-upper arm circumference (MUAC), and triceps skinfold (TSF) were measured according to ISAK guidelines[23] using a stadiometer with a balance-beam scale (Seca 220, Seca, Hamburg, Germany), a 2-meter anthropometric tape and a segmometer (Cescorf, Rio Grande do Sul, Brazil) with 0.1-cm precision, and a skinfold caliper (Cescorf) with 0.1-mm precision, a jaw width of 88 mm, and jaw pressure of 10 g/mm^2. BMI was calculated by dividing body weight (kilograms) by the square of the height (meters), the WC/HC ratio (W/H ratio) was calculated by dividing WC by HC, and arm fat index (AFI) was calculated by dividing the mid-upper arm fat area (MUAFA) by the mid-upper arm area (MUAA) and multiplying by 100. MUAA and MUAFA were calculated as follows: MUAA (cm) = MUAC (cm)^2/4π; and MUAFA (cm) = MUAA – (π × TSF)^2/4π.

Maximal stress test and training eligibility

The eligibility for WT and determination of aerobic fitness of participants were assessed based on the Astrand protocol through a graded maximal test on a cycle ergometer (Sana Bike 150 F, ergosana GmbH, Bitz, Germany). During the stress test, heart rate and rhythm control were monitored by continuous electrocardiography (AT-10 plus, Schiller, Baar, Switzerland), and blood pressure was also monitored continuously. The AT-10 plus provided information about the duration and maximal intensity of the test, expressed in metabolic equivalents, and the maximal power level, expressed in Watts. Maximal oxygen uptake (VO_{2max}) was estimated[24] by multiplying the maximal metabolic equivalents by 3.5.

The physical exercise program

Subjects assigned to NW received training for 1 week with an instructor licensed by the Associazione Nordic Walking Italia on how to use the proper technique, according to the guidelines of the International Nordic Walking Association, whereas the WT group simply trained for 40 min. At the end of the lessons for the NW technique, both groups started walking at moderate intensity. Exercise intensity was monitored based on a 15-category scale of the ratings of perceived exertion. Duration, intensity, frequency and progression are presented in Figure 1. The participants became familiar with the scale before and during the maximal stress test and then during the first week of training. At least two of the three weekly sessions were supervised. Physical exercise was the only study intervention.

Statistical analysis

Data analyses were designed to assess whether differences in VEGF levels and body attribute measures between the WT and NW groups were evident after 13 weeks of training. To test the effects of WT vs. NW training, a two (group) × two (time) repeated-measures multivariate analysis of variance (RM-MANOVA) was carried out with VEGF and anthropometric measures (body weight, BMI, WC, HC, W/H ratio, and AFI) as dependent variables and groups as independent variables. Furthermore, a RM-MANOVA was also carried out with VEGF and VO_{2max} as dependent variables and groups as independent variables. Before statistical analysis, data were checked to ensure that the assumptions for RM-MANOVA were satisfied[25]. Triceps skinfold was not analyzed because this test did not satisfy at least one of the assumptions for RM-MANOVA. Furthermore, independent-sample *t*-tests were used to compare groups before and after 13 weeks of training. Paired-sample *t*-tests were used to assess the effect of training for each group, separately. Significance cut-off points were

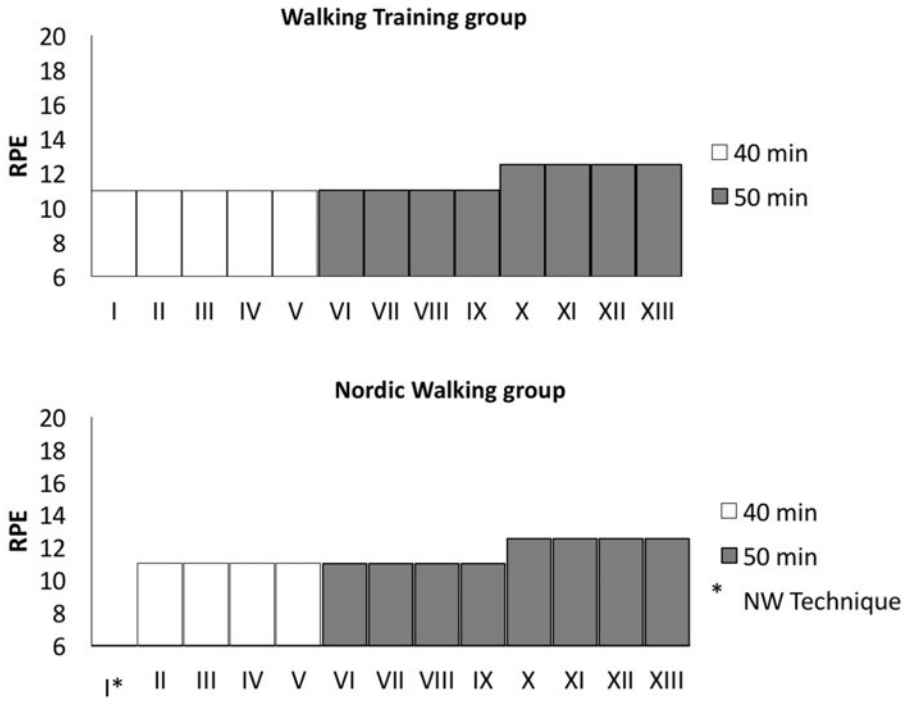

Figure 1. Physical exercise program. RPE: rate of perceived exertion; white bars: duration 40 min; gray bars: duration 50 min. *Nordic Walking technique, three lessons of 90 min. Both groups performed three times per week, with 5–10 min of warm up and 5–10 min of cool down.

adjusted at $p < 0.025$ to account for multiple comparisons[25]. Cohen's *d* was used to assess both between-group and within-group differences and interaction effects[25], considering a value of 0.2 as small, 0.5 as medium and 0.8 or above as large. SPSS 12.0 (SPSS®, Chicago, IL, USA) was used for data analysis whereas G*Power 3.0.10 was used for Cohen's *d* calculation.

Results

Baseline characteristics and correlations

Physiological and anthropometrical characteristics of the participants are presented in Table 1. The women were moderately overweight based on BMI, and they were at increased risk for cardiovascular and metabolic diseases based on WC alone[26] and combined with BMI[27]. Furthermore, aerobic fitness was poor on average, based on VO_{2max} values. Concerning basal correlations, VEGF was directly correlated with BMI ($r = 0.387$, $p = 0.035$) and TSF ($r = 0.440$, $p = 0.015$).

Effect of WT and NW on VEGF level and body attributes

Anthropometry and VEGF measurements were performed with WT and NW participants both prior to training and after 13 weeks of aerobic training. Results of the multivariate and univariate analyses are presented in Table 2. Briefly, RM-MANOVA confirmed that there were significant multivariate effects for the type of training (NW vs. WT), for the training itself (NW or WT), and for the interaction between training type and baseline/13-week training (Table 2). Univariate between-group analyses revealed that WT participants had higher values for AFI compared with NW participants (Figure 2(E)). Within-group univariate analyses indicated that the VEGF level increased significantly between baseline and week 13 (Figure 2(A)), whereas weight (Figure 2(B)), BMI (Figure 2(C)), HC (Figure 2(D)), and AFI (Figure 2(E)) decreased significantly, irrespective of training type. There was a significant interaction between training type and baseline/13-week training for VEGF, W/H ratio, and AFI but not for other variables. Further analyses of interaction for VEGF, W/H ratio, and AFI revealed that VEGF increased in the NW group ($t(14) = -2.90$, $p = 0.012$) but not in the WT group (Figure 2(A)). Furthermore, although WT participants had a higher mean AFI value at baseline ($t(28) = 4.13$, $p < 0.001$), there was no difference between the NW and WT groups by week 13 (Figure 2(E)); both groups exhibited a decrease in AFI, but the reduction was greater for the WT group ($t(14) = 5.533$, $p < 0.001$) than NW ($t(14) = 2.568$, $p = 0.022$) (Figure 2(E)). In contrast, there was no difference in the W/H ratio at baseline, although WT participants had a higher average value by week 13 ($t(28) = 3.39$, $p < 0.024$) (Figure 2(F)).

Finally, RM-MANOVA confirmed that there was a significant multivariate effect for 13 weeks of training when VO_{2max} and VEGF were analyzed together ($V = 0.288$, F 0(2, 27) = 5.45, $p = 0.010$, $d = 0.64$). Within-group univariate analyses indicated

Table 1. Physiological and anthropometrical characteristics of the study population.

	Mean ± standard deviation
Age (years)	57.9 ± 3.6
Weight (kg)	64.5 ± 10.4
Height (cm)	157.3 ± 6.1
Body mass index (kg/m^2)	26.1 ± 4.7
Waist circumference (cm)	82.8 ± 10.5
Hip circumference (cm)	101.5 ± 8.2
Waist-to-hip ratio	0.8 ± 0.1
Triceps skinfold (mm)	25.3 ± 6.8
Arm fat index	45.8 ± 7.3
VO_{2max} (ml/kg/min)	22.9 ± 3.5

VO_{2max}, maximal oxygen uptake.

Table 2. Effect of walking training (WT) and Nordic walking (NW) on circulating vascular endothelial growth factor (VEGF) level, body attributes, and cardio-respiratory fitness.

Measures	*Source*	*V*	*F*	*d.f.*	*p*	*d*
VEGF, body weight, BMI, WC, HC, W/H ratio, AFI	Type of training (NW vs. WT)	0.48	2.91	2, 27	0.026	0.96
	Training itself (baseline vs. week 12)	0.73	8.34	2, 27	<0.001	1.63
	Training itself × training type	0.47	2.80	2, 27	0.030	0.94
VEGF	Type of training (NW vs. WT)		0.18	1, 28	0.678	0.25
	Training itself (baseline vs. week 12)		7.60	1, 28	0.010	0.52
	Training itself × training type		4.60	1, 28	0.041	0.41
Body weight	Type of training (NW vs. WT)		0.95	1, 28	0.337	0.18
	Training itself (baseline vs. week 12)		5.81	1, 28	0.023	0.46
	Training itself × training type		0.09	1, 28	0.761	0.05
BMI	Type of training (NW vs. WT)		2.59	1, 28	0.119	0.09
	Training itself (baseline vs. week 12)		5.68	1, 28	0.024	0.45
	Training itself × training type		0.27	1, 28	0.639	0.30
WC	Type of training (NW vs. WT)		3.88	1, 28	0.059	0.37
	Training itself (baseline vs. week 12)		2.48	1, 28	0.127	0.30
	Training itself × training type		2.12	1, 28	0.156	0.27
HC	Type of training (NW Vs WT)		1.22	1, 28	0.278	0.21
	Training itself (baseline Vs. week 12)		12.64	1, 28	0.001	0.67
	Training itself × training type		2.42	1, 28	0.131	0.29
W/H ratio	Type of training (NW vs. WT)		3.88	1, 28	0.059	0.37
	Training itself (baseline vs. week 12)		1.05	1, 28	0.314	0.19
	Training itself × training type		7.48	1, 28	0.011	0.29
AFI	Type of training (NW vs. WT)		10.71	1, 28	0.003	0.63
	Training itself (baseline vs. week 12)		37.05	1, 28	0.001	1.15
	Training itself × training type		13.16	1, 28	0.001	0.42

BMI, body mass index; WC, waist circumference; HC, hip circumference; W/H, waist-to-hip ratio; AFI, arm fat index; V, Pillai's Trace multivariate outcome.

that VO_{2max} increased significantly between baseline and week 13 ($F(1, 28) = 5.31$, $p = 0.029$, $d = 0.43$) (Figure 2(G)).

Discussion

Several studies have indicated that physical exercise induces VEGF release from skeletal muscle. Indeed, muscle contraction leads to an increase in both cellular VEGF mRNA content[28] and vesicle density in the subsarcolemmal region as well as an increase in VEGF level in the muscle interstitium[14]. Furthermore, physical exercise-induced shear stress determines VEGF release from muscle endothelial cells[12]. Conflicting results have emerged among various studies concerning circulating VEGF level in response to physical exercise. Although there are evidences that VEGF is mainly secreted locally for muscle angiogenesis, it has recently been suggested that factors released in the bloodstream, including VEGF, may induce positive effects on distant non-working muscles and tissues[29]. Various studies have shown that physical exercise increases the level of circulating VEGF[15–17], but other studies have shown no such effect of physical exercise – or indeed have shown a net decrease in VEGF level[30,31]. These differences may be ascribed to several factors such as differences in experimental protocols, the reported high interindividual differences in VEGF response[16], and the fact that better-trained individuals are more responsive to physical exercise with respect to VEGF release. Wahl and colleagues[15,16] reported that both acute and chronic high-intensity interval training elicit a significant increase in circulating VEGF, whereas low-intensity/high-volume training does not. These investigators suggested that both mechanical and metabolic stimuli are greater during high-intensity interval training, leading to a greater release of VEGF from muscle into the circulation. However, high-intensity interval training protocols are suitable for athletes and healthy subjects but may be less appropriate for postmenopausal women because most of them are physically inactive[21] and thus have poor physical fitness. On the other hand, a series of studies in humans revealed that the increase in muscle interstitial VEGF is independent of intensity at submaximal levels of physical exercise, as evidenced by the increase of VEGF when legs were passively moved[19], suggesting that mechanical signals may predominate when metabolic pathways are not strongly stimulated – such as during low-intensity/high-volume training. Hence, poor involvement of metabolic stimuli probably underscores the observed small release of VEGF into the circulation, an aspect that may explain the lack of significant VEGF changes in some studies that adopted typical endurance training protocols. On the other hand, our result suggest that the muscle groups involved in physical exercise could be an important parameter to be manipulated, e.g. with NW training. Indeed, in addition to VEGF levels, a previous study from Febbraio and colleagues[32] showed that also the release of muscular IL-6 is affected by the number of the muscle groups involved in physical exercise, regardless of the work intensity, and it is possible that several other exercise-induced factors may produce similar responses.

It is well established that adipocytes also produce VEGF[22]. Consequently, the effect of training on VEGF has been studied with respect to aspects of body composition. In the present study, the VEGF level correlated directly with BMI and triceps skinfold at baseline. Weight, BMI, WC, and W/H ratio were similar between subgroups at baseline, whereas AFI was higher in the WT group at baseline. After training, both groups experienced a slight decrease in four body measures (weight, BMI, HC, AFI), while there was no correlation with VEGF. These results suggest that adipose tissue is, initially at least, the main source of VEGF because participants before training were mostly physically inactive; after training, however, the primary production of VEGF shifted to

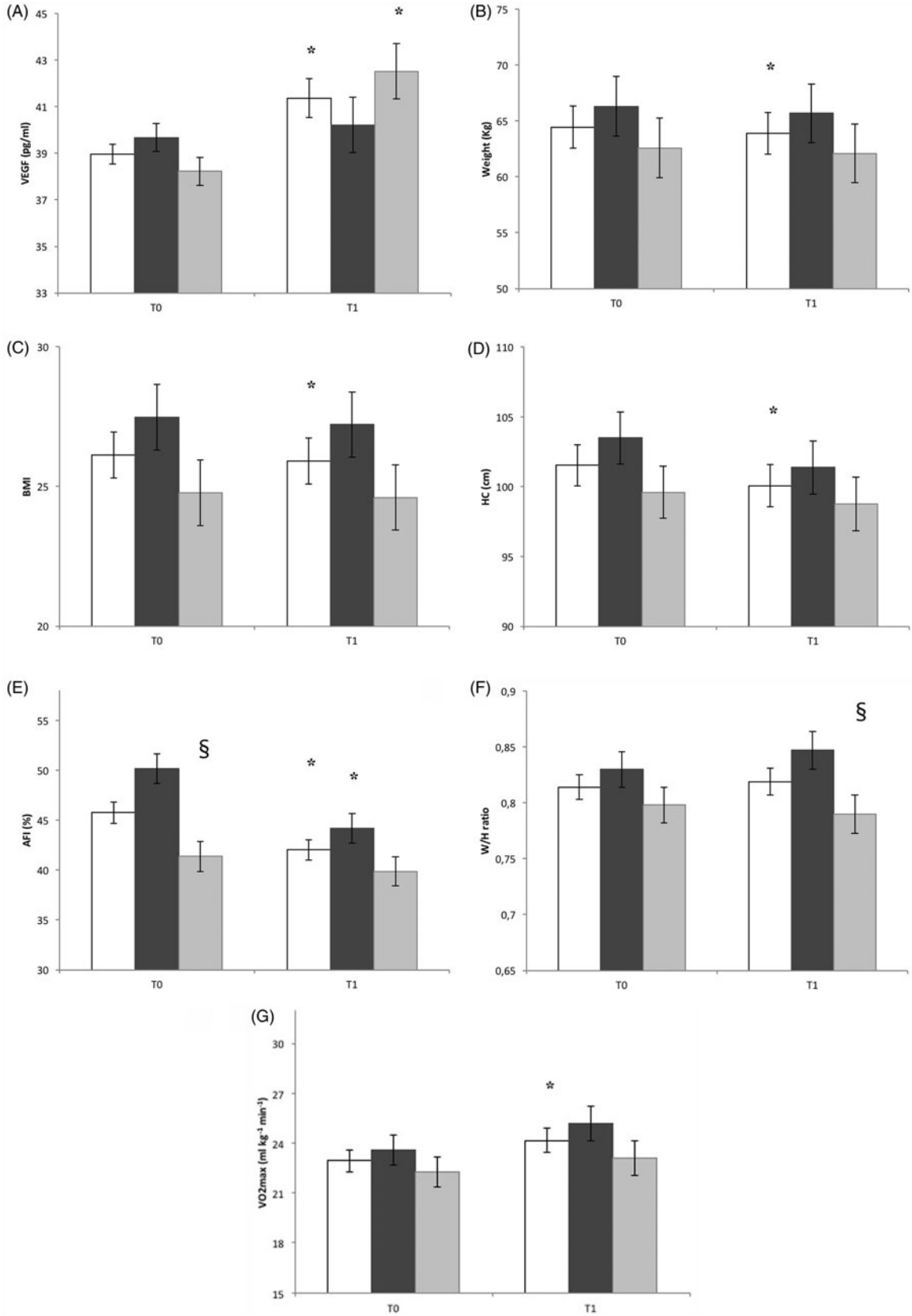

Figure 2. Differential effects of Nordic walking (NW) and walking training (WT) on (A) vascular endothelial growth factor (VEGF); (B) weight; (C) body mass index (BMI); (D) hip circumference (HC); (E) arm fat area (AFI); (F) waist-to-hip ratio (W/H); (G) maximal oxygen uptake (VO_{2max}). White bars: main effect for 13 weeks of training (irrespective of training type group); dark-gray bars: WT group; light-gray bars: NW group. *, Significant difference from T_0 to T_1; §, significant difference between groups.

skeletal muscle, and thus the contribution of adipose tissue probably decreased or did not change. Although AFI decreased much more in the WT participants than in the NW participants (12% and 4%, respectively) and the W/H ratio was 10% greater for the WT group than the NW group after training, the remaining body attributes did not differ in both their trends and absolute values, and it is then unlikely that differences in VEGF levels between groups were affected by only these differences in localized adiposity. Furthermore, previous studies indicated that visceral fat is one of the main sources of VEGF[33], but, in a study in which computed tomography scanning was used to measure fat mass, subcutaneous fat correlated with VEGF whereas visceral fat did not[34]. Then, if we consider subcutaneous fat as a main source of VEGF, the observed greater decrease in AFI in our WT participants would suggest that the relatively smaller increase in circulating VEGF for this group could also be attributable to a decrease of an important source such as subcutaneous adipose tissue while the greater W/H ratio of the same group should induce a greater VEGF release. This suggests the improbability that the observed differences in VEGF release between the WT and NW groups could be explained by changes in AFI or differences in the W/H ratio.

Finally, because aerobic training improves athletic performance, the VEGF level may also be related to differences in cardiorespiratory fitness. However, both the NW and WT groups exhibited a significant increase in VO_{2max}, with no significant difference between these groups. This lack of difference is likely attributable to the fact that, whereas NW participants used a larger overall body muscle mass during their training, the WT group probably walked at a higher average speed to reach the same intensity. This result supports our conclusion that NW promotes a greater release of VEGF owing to the involvement of a larger muscle mass, regardless of exercise intensity.

The main limitation of the study is that it was conducted with only postmenopausal women. Then, we are not able to assert whether the evidence from this study can be extended to other populations such as men, younger people, athletes, and pathological individuals. A second limitation is that subgroups were unbalanced in AFI values although they were in the same range of BMI, WC, and W/H ratio, which are the most important health-related body measures. Under this point of view, the present study offers a more comprehensive understanding of the effect of physical exercise on the association between VEGF and body fat.

In conclusion, this study indicates that, in postmenopausal women, the amount of muscles involved during exercise may dictate the magnitude of endocrine release of VEGF by skeletal muscle and muscle endothelium. This evidence may have important repercussions because the number of muscles involved in physical exercise can be a useful parameter to be manipulated, e.g. with NW training, to optimize the release of factors that affect health. The practice of NW seems particularly appreciated by postmenopausal women because it is perceived as feasible and safe[9] and the perceived exertion is lower in comparison with normal WT, allowing to maintain a given intensity without affecting adherence to the training protocol[35]. This is particularly important in specific groups with poor fitness, such as obese women, who are prone to desist with physical exercise when they perceive high-intensity training as unpleasant[36], or breast cancer survivors, who have low fatigue tolerance, in whom NW effectiveness was recently demonstrated[37].

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Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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