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Effect of exercise training combined with phytoestrogens on adipokines and C-reactive protein in postmenopausal women: a randomized trial

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ABSTRACT

Phytoestrogens and training could be effective to reduce cardiovascular and type 2 diabetes mellitus risk factors in postmenopausal women. Nevertheless, the impact of their combination on adipokines and systemic inflammation was never investigated. The objective was to verify if 6 months of mixed training combined with phytoestrogens could have an additional effect on adipokine levels and systemic inflammation in obese postmenopausal women. Fifty-two obese women aged between 50 and 70 years were randomly assigned to (1) exercise with placebo (EX + PL; n = 25) or (2) exercise with phytoestrogens (EX + PHY; n = 27). Body weight, waist circumference, fat mass, and lean body mass (dual-energy x-ray absorptiometry) were assessed. Fasting plasma glucose and insulin, adiponectin, leptin, and C-reactive protein (CRP) levels were obtained after a 12-hour overnight fast. Total energy intake was measured with a 3-day dietary record. All measurements were performed before and after the 6-month intervention. Although energy intake remained unchanged, body composition was improved in all women (all *P*s < .02). Plasma CRP and leptin levels decreased in both groups similarly (all *P*s < .03), whereas plasma adiponectin and insulin did not change with exercise combined with placebo or phytoestrogens. Correlation analyses showed that homeostasis model assessment of insulin resistance ($r = -0.58$, $P = .02$) and fasting insulin levels ($r = -0.42$, $P = .02$) at baseline were both correlated with changes in leptin levels. Baseline fasting glucose ($r = -0.36$, $P = .03$) and adiponectin ($r = 0.45$, $P = .005$) levels were associated with changes in CRP concentrations. Although mixed exercise program combined with phytoestrogens does not seem to provide any additional effect, mixed training improves systemic inflammation and leptin concentrations in obese postmenopausal women.

Trial Registration at: http://www.clinicaltrials.gov. Trial registration number: NCT01048606.

Contribution of each author: ER: data collection, analyses, figure preparation, and manuscript preparation; SC: study design, data collection, and manuscript preparation; MA and JL: data collection and manuscript preparation; DT: coinvestigator, data collection, and manuscript preparation; IJD: principal investigator, senior writer, study design, and manuscript preparation.

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1. Introduction

With the aging of the population and the burden of obesity-related chronic diseases such as type 2 diabetes mellitus and cardiovascular disease, health care costs will rise in the next years [1]. In this context, excess adiposity, especially in abdominal area, associated with a higher risk of chronic diseases in postmenopausal women [2], represents a major health issue.

Adipose tissue was formerly considered as a storage organ of free fatty acids, but is now recognized as an active endocrine tissue by producing at least 30 peptides and proteins, collectively named *adipokines* [3]. The latter play a central role in lipid and glucose metabolism and thus are involved in the development of chronic diseases [4]. In fact, with an excess adiposity, some factors such as leptin and C-reactive protein (CRP) are overproduced, whereas levels of adiponectin are reduced [5]. Even if the mechanism remains unclear, leptin and adiponectin have already been associated with insulin resistance [6,7] and cardiovascular disease markers [8,9] in postmenopausal women. Leptin to adiponectin ratio (LAR) was also reported as a better marker for metabolic disease [10] and insulin resistance [11] than adiponectin or leptin alone in aging individuals. Through those metabolic alterations, it could also potentially induce systemic inflammation [12] and indirectly modulate CRP [13], which has also been associated with both type 2 diabetes mellitus [14] and cardiovascular disease [15]. Hence, these adipokines may be considered as nontraditional cardiovascular risk factors; and their regulation in postmenopausal women should be of prime interest.

During the last few years, with the controversy about hormone replacement therapy, numerous women and their physician sought for alternative strategies such as phytoestrogens and/or exercise to reduce cardiovascular risk factors. We previously showed that exercise combined with phytoestrogens did not have synergic effect on classic cardiovascular risk factors [16]. Although few studies have investigated the effects of phytoestrogen supplementation on adipokine levels or inflammatory markers, Charles et al [17] and Llaneza et al [18] showed that adiponectin levels in postmenopausal women increased with a phytoestrogen supplementation. Leptin concentrations have also been shown to be increased [18,19], although some controversial results have been reported [17]. Finally, whereas CRP remained unchanged with phytoestrogens, tumor necrosis factor–α level was reduced in postmenopausal women [18].

Moreover, exercise is now considered as a key component of obesity therapy [20]; and previous studies have reported that exercise could improve metabolic profile by reducing leptin resistance [21-23] and systemic inflammation [21,24,25]. We suggest that exercise and phytoestrogens may interact to induce beneficial alterations of adipokine and inflammation levels because (1) both phytoestrogens and exercise have received support to improve type 2 diabetes mellitus and cardiovascular risk profile in postmenopausal women and (2) they have shown to act in synergy to induce significant loss in abdominal fat [26]. In this regard, the purpose of this study was to verify the effect of 6 months of mixed exercise combined or not with phytoestrogens on adiponectin, leptin, and CRP levels in overweight to obese sedentary postmenopausal women.

2. Methods

2.1. Subjects

Fifty-two postmenopausal women aged between 50 and 70 years were recruited by advertisements in local newspapers to participate in a randomized controlled study. All women had to meet the following criteria: white, absence of menses for the past 12 months, overweight or obese (body mass index [BMI] 28-40 kg/m^2 or waist circumference >88 cm), healthy, without major physical incapacity, without hormone replacement therapy (off for ≥1 year), sedentary (no participation in a systematic/supervised exercise program during the last 5 years), weight stable (±2 kg) for the last 6 months, nonsmoker, moderate drinker (<15 g of alcohol per day), no medication that influences glucose or lipid metabolism, and without isoflavones supplementation (off for ≥1 year).

2.2. Experimental protocol and study design

The experimental design was approved by the Ethics Committee of the Geriatric Institute of the University of Sherbrooke (CSSS-IUGS). All participants gave their written informed consent to participate in the study during the first visit to the Research Centre on Aging (CSSS-IUGS). After a 12-hour fast, body composition and anthropometric measurements, and a 2-hour oral glucose tolerance test (OGTT) were performed. Afterward, subjects were randomly assigned to 1 of 2 groups: (1) exercise and placebo (EX + PL; n = 25) and (2) exercise and phytoestrogens (EX + PHY; n = 27). Measurements were repeated after 6 months, with at least 3 to 5 days of rest after the last training session.

2.3. Randomization

Arkopharma (Arkopharma, Carros, France) provided the treatment capsules and assigned a treatment (PHYTO or placebo) to each subject's number based on a pattern that was kept blind from us. We thus received the capsule containers identified by the subject number and accompanied by a sealed individual envelope that contained the nature of treatment. The envelopes were kept under key by the principal investigator until the end of the study, thus ensuring the double-blind nature of the trial.

2.4. Phytoestrogen supplementation

Subjects ingested 4 capsules daily, containing either soy phytoestrogens or placebo (Arkopharma). Each phytoestrogen capsule contained 325 mg of soy extract with 17.5 mg of isoflavones. The 70-mg daily dose (4 daily capsules of 17.5 mg of isoflavones) contained 44 mg of daidzein, 16 mg of glycitein, and 10 mg of genistein. Placebo contained cellulose. To verify compliance, participants were asked to bring back their supplementation bottle every month to have a new one, as previously described [27].

2.5. Mixed exercise program

The 6-month program consisted of 3 mixed (aerobic and resistance) exercise sessions per week, as previously described [16]. Each session lasted for 1 hour and consisted of 30 minutes of resistance training and 30 minutes of aerobic exercise. To be included in analyses, subjects had to attend a minimum of 85% of all sessions; that is, women had to attend a minimum of 67 of 78 sessions. Resistance training included movements from all major muscle groups using free weight and selective-plate machines (Life Fitness, Schiller Park, IL). The intensity was increased on a monthly basis, from 60% of maximal strength (measured as 1 repetition maximum) during the first month to 85% during the sixth month. Aerobic exercise was performed on an ergocycle and a treadmill using a protocol that closely followed the American College of Sports Medicine's guidelines for sedentary adults [28]. Training started at 40% to 50% of heart rate reserve and increased up to 70% to 85%, where heart rate reserve was computed using the Karvonen formula [29]. Training heart rate was then established with the following equation: heart rate reserve × percentage training target + resting heart rate.

After 3 months of training, continuous aerobic training was alternated with interval training. Interval training consisted of alternating periods of 4-minute high intensity (≥90% of heart rate reserve) and periods of 3-minute active recovery (50%-65% of heart rate reserve) [30]. All training sessions were closely supervised by a kinesiologist.

2.6. Anthropometrics and body composition measurements

Body weight was determined to the nearest 0.2 kg by an electronic scale (SECA 707, Hamburg, Germany), and standing height was measured using a wall stadiometer (Takei, Tokyo, Japan) [26]. Waist circumference (±0.1 cm) was measured using a tape measure as previously described [16]. Fat mass (FM) and lean body mass (LBM) were assessed in a supine position using dual-energy x-ray absorptiometry (GE Prodigy Lunar, Madison, WI) as described in a previous study from our laboratory [26].

2.7. Glycemic parameters

After a 12-hour overnight fast, a 75-g OGTT was performed to collect blood samples in EDTA-containing Vacutainer tubes through a catheter from an antecubital vein at –15, 0, 30, 60, and 120 minutes. Blood samples were immediately centrifuged to separate plasma, which was thereafter stored at –80°C until analyses, for measurement of plasma adiponectin and leptin levels. Plasma glucose and insulin concentrations were analyzed at the Sherbrooke University Hospital Center (CHUS) by enzymatic and immunologic method, respectively (coefficients of variation were between 1.8% and 2% for glucose and <10% for insulin). Insulin sensitivity based on the "homeostasis model assessment" (HOMA) index was evaluated according to the following equation [31]: insulin (micro–international units per milliliter) × glucose (millimoles per liter)/22.5. Finally, glucose areas under the curve (AUCs) during OGTT were calculated with the trapezoid method.

2.8. Adipokines and CRP analyses

After a 12-hour overnight fast, blood samples were obtained in the morning by an experienced nurse. Plasma CRP was analyzed at the CHUS by immunoturbidimetry method (MODULAR; Roche Diagnostic, Toronto, Ontario, Canada). Plasma adiponectin and leptin were measured in our laboratory (Victor V; Perkin-Elmer, Woodbridge, Ontario, Canada) by enzyme-linked immunosorbent assay using monoclonal antibodies specific for human adiponectin (Invitrogen Life Technologies, Woodbridge, Ontario, Canada) and leptin (ALPCO Diagnostics, Salem, NH). The intra- and interassay coefficients of variation were, respectively, 0.9% and 9.8% for adiponectin and 5.7% and 9.9% for leptin. Regarding CRP, coefficient of variation from the CHUS laboratory was 2.5%. Finally, LAR was also calculated [10].

2.9. Dietary intake

During the 6-month intervention period, subjects were asked to maintain their usual dietary habits. As previously described, subjects were asked to complete a 3-day dietary record before and after the study [16]. Daily energy intake was analyzed using Nutrifiq software (Laval University, Québec).

2.10. Statistical analyses

Results are given as means (95% confidence interval) in tables and means ± standard error in figures. The Kolmogorov-Smirnov test was applied to verify the normal distribution of each variable of interest. Between-groups comparisons at baseline were verified with an independent Student *t* test for normally distributed variables (FM, glucose and log-transformed insulin and adiponectin levels, leptin levels, LAR, glucose AUC, and total energy intake) and a nonparametric Mann-Whitney *U* test for nonnormally distributed variables (total body weight, LBM, waist circumference, and CRP levels). Repeated-measure analyses of variance (2 × 2) were used to verify the effect of 6 months of exercise combined with placebo or phytoestrogens for normally distributed variables. If there was an interaction (time × group), we used paired *t* test to verify the effect of 6 months of exercise in each group separately. Nonparametric Wilcoxon signed rank test followed by a Mann-Whitney *U* test (to compare changes between groups) was used when appropriate (not normally distributed variables). Pearson correlation coefficients and Spearman ρ were used as appropriate to quantify the association between variables. Variables significantly associated with changes in leptin and CRP were tested for independency by multivariate stepwise regression analyzes. All analyzes were performed using SPSS 15.0 program for windows (SPSS, Chicago, IL). Statistical significance was set at $P < .05$.

3. Results

3.1. Group comparisons

As shown in Table 1, the EX + PL and EX + PHY groups were similar for all variables at baseline.

Table 1 – Characteristics of postmenopausal women included in this study at baseline

	EX + PL n = 28	EX + PHY n = 27	P value
Age (y)	56.2 (52.7-59.7)	60.1 (57.9-62.3)	.52
Estradiol (pg/mL)	109.4 (63.0-155.8)	70.6 (40.2-101.0)	.45
Weight (kg)	77.1 (71.8-82.3)	79.6 (73.5-85.7)	.56
BMI (kg/m^2)	28.8 (25.2-32.4)	29.1 (27.4-30.8)	.42
FM (kg)	32.5 (25.4-39.5)	31.5 (27.8-35.3)	.83
LBM (kg)	41.9 (36.0-47.8)	40.8 (38.0-43.6)	.42
Waist circumference (cm)	99.1 (92.0-106.2)	96.4 (90.1-102.7)	.84
Glucose (mmol/L)	4.6 (4.1-5.1)	4.5 (4.1-5.0)	.62
Insulin (pmol/L)	40.1 (20.7-59.5)	38.7 (25.2-52.2)	.73
HOMA-IR	1.2 (0.5-2.0)	1.2 (0.7-1.6)	.65
AUC glucose (mmol/[L min])	1368.7 (1080.5-1656.9)	1487.8 (1239.3-1736.3)	.67
Total energy intake (kcal/d)	1845.7 (1666.3-2025.2)	2010.7 (1829.3-2192.1)	.30
Adiponectin (μg/mL)	21.3 (18.6-24.0)	20.3 (17.7-23.0)	.32
Leptin (ng/mL)	39.3 (31.6-47.0)	41.4 (34.2-48.5)	.69
LAR	1.91 (1.33-2.49)	2.69 (1.75-3.63)	.17
CRP (mg/L)	6.3 (2.2-10.4)	4.8 (3.7-5.9)	.57

Values are means (95% confidence interval).

Total energy intake, measured with a 3-day dietary record, remained unchanged after 6 months of intervention in all subjects.

As published elsewhere [16], whereas total body weight remained unchanged (EX + PL: $P = .42$; EX + PHY: $P = .08$), FM as well as waist circumference decreased (all Ps < .02) and LBM increased (EX + PL: $P = .01$; EX + PHY: $P = .005$) in both groups similarly. Although fasting insulin levels, glucose AUC, and HOMA-IR did not change (all Ps > .38), fasting glucose concentrations increased after the intervention in both groups ($P = .01$).

Finally, as shown in Fig. 1, leptin concentrations decreased in exercising postmenopausal women ($P = .001$), irrespective of the phytoestrogen supplementation or placebo. Likewise, CRP levels were similarly reduced in both groups (EX + PL: $P = .03$; EX + PHY: $P = .009$) after 6 months of intervention, whereas plasma adiponectin levels remained unchanged in both groups. Analyses revealed that LAR tended to change in both groups ($P = .058$).

3.2. *Relationships between body composition, glucose metabolism markers, and adipokines*

Correlation analyses showed that plasma leptin was associated with baseline values for FM ($r = 0.73$, $P < .0001$), waist circumference ($r = 0.61$, $P < .0001$), LBM ($r = 0.36$, $P = .01$), and fasting insulin level ($r = 0.53$, $P < .0001$). Nevertheless, the relationship between leptin levels and waist circumference as well as LBM disappeared after correcting for FM. Moreover, CRP concentrations were positively associated with FM ($r = 0.31$, $P = .03$) and negatively with adiponectin levels ($r = -0.38$, $P = .005$). Conversely, we did not observe any correlations between adiponectin levels and body composition or

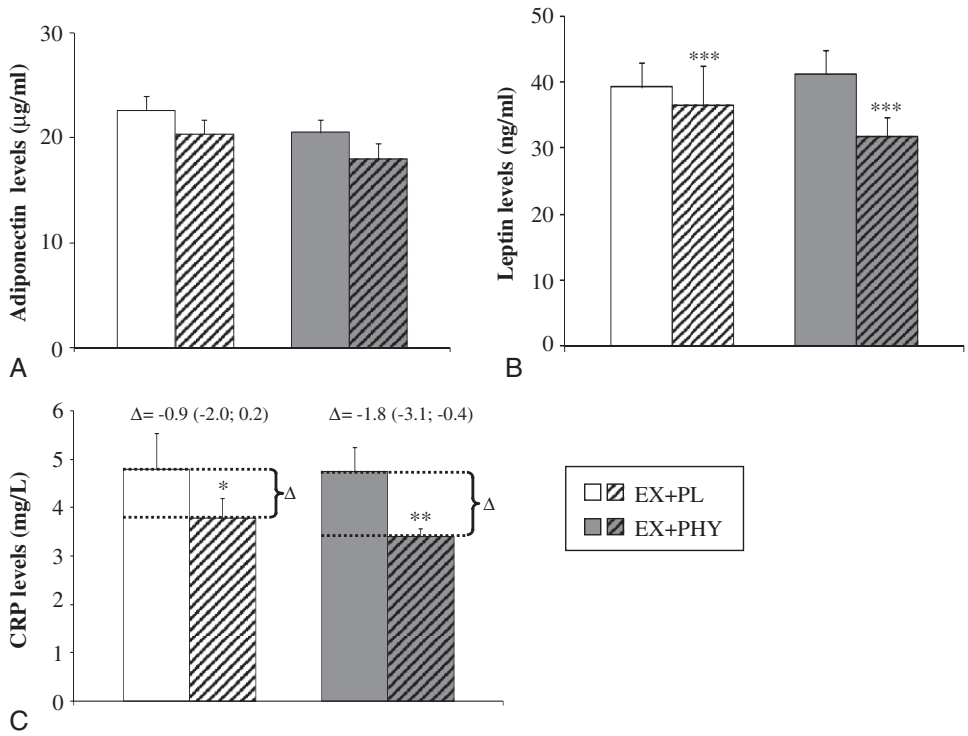

Fig. 1 – Effect of mixed training combined with placebo or phytoestrogens on plasma adipokines and CRP levels. *P < .05; **P ≤ .01; ***P ≤ .001: significantly different from baseline values. As analysis for CRP levels was performed with nonparametric tests, we also present changes for each group where Δ = mean (95% CI).

Table 2 – Relationships between intervention-related changes in some nontraditional factors and baseline values of body composition and glucose homeostasis factors

	Δ Leptin	Δ LAR	Δ CRP
Adiponectin	0.33	0.58‡	0.45†
Leptin	−0.65§	−0.54†	−0.23
CRP	−0.01	0.03	−0.89§
Glucose	−0.40*	−0.46†	−0.36*
Insulin	−0.52†	−0.45*	−0.29
HOMA-IR	−0.58‡	−0.53†	−0.34‖
FM	−0.48†	−0.27	−0.31
LBM	−0.41*	−0.16	−0.15

* $P < .05$: significant correlation.
† $P \leq .01$: significant correlation.
‡ $P \leq .001$: significant correlation.
§ $P \leq .0001$: significant correlation.
‖ $P = .06$: tendency for a significant correlation.

glucose metabolism markers at baseline. Finally, LAR was positively associated with fasting glucose ($r = 0.39$, $P = .02$), fasting insulin ($r = 0.61$, $P < .0001$), and HOMA of insulin resistance (HOMA-IR) ($r = 0.64$, $P < .0001$) at baseline.

As shown in Table 2, although correlation analyses indicated that FM ($r = -0.48$, $P = .006$), fasting insulin levels ($r = -0.52$, $P = .004$), and HOMA-IR ($r = -0.58$, $P = .001$) at baseline were negatively correlated with leptin levels reduction, stepwise linear regression revealed that initial HOMA-IR was the only independent predictor explaining the decrease in leptin ($r^2 = 0.34$, $P = .001$). Furthermore, LAR changes were associated with baseline values of fasting glucose ($r = -0.46$, $P = .01$), fasting insulin ($r = -0.45$, $P = .02$), and HOMA-IR ($r = -0.53$, $P = .003$). Stepwise linear regression analyses showed that HOMA-IR and fasting insulin at baseline explained 41% of LAR variation ($r^2 = 0.41$, $P = .001$). On the other hand, even if baseline fasting glucose ($r = -0.36$, $P = .03$) and adiponectin ($r = 0.45$, $P = .005$) levels were associated with CRP concentration decrease, neither of them were independent factors explaining CRP changes.

Finally, the decrease in leptin and CRP levels was not associated with changes in body composition or plasma glucose levels.

4. Discussion

The main objective of this study was to verify if mixed training combined with phytoestrogens could have an effect on plasma concentrations of 2 main adipokines and systemic inflammation in obese postmenopausal women. In this regard, our results showed that the addition of phytoestrogens did not enhance beneficial effects of aerobic and resistance exercises program on some nontraditional cardiovascular risk factors in obese postmenopausal women.

When compared with those of lean postmenopausal women [32], baseline leptin levels of this study's sample fell in a higher range. The same applies for CRP concentration compared with that of lean postmenopausal women [33]. Altogether, these observations suggest leptin resistance and silent inflammation. Our results support that obese postmenopausal women are at higher risk of chronic diseases [2].

To the best of our knowledge, this is the first randomized study to verify the impact of the combination of phytoestrogens and exercise training on adipokine concentrations in overweight to obese postmenopausal women. Regarding plasma adiponectin, our results showed that mixed exercise program combined with placebo or phytoestrogens did not seem sufficient to induce any changes. This is in agreement with previous studies reporting that neither aerobic [34] nor mixed training [35] could increase adiponectin concentrations in aging individuals. On the other hand, results about the effect of phytoestrogen supplementation (with 160 mg of isoflavones) on adiponectin levels are inconsistent. Actually, whereas Charles et al (2009) [17] reported a slight increase, others showed that adiponectin levels remained unchanged in postmenopausal women [36]. The fact that the study of Christie et al (2010) [36] included white and African women could partly explain this difference. Nevertheless, Llaneza et al (2010) [18] showed that 6 months of soy isoflavones combined with moderate aerobic exercise training and a 1200-kcal diet seemed to have an additional effect on adiponectin levels in healthy, obese, postmenopausal women. Of note, however, isoflavones amounts were very close to the ones used in our study; but the composition of phytoestrogen supplementation was very different. In fact, whereas genistein was 6-fold lower, daidzein and glycitein amounts were 3- to 5-folds higher in our study. Hence, the composition of phytoestrogens supplementation may be an explanatory factor. Moreover, to increase adiponectin level with mixed training and phytoestrogens, it is possible that a certain level of weight loss is necessary. Although our results did not support any additional effect of mixed exercise program combined with phytoestrogens, they showed a positive impact of mixed training on elevated leptin levels and systemic inflammation in overweight to obese postmenopausal women. In fact, leptin levels were reduced by approximately 18% and CRP levels by 16% following the exercise program. Knowing that a recent study showed that mixed training seems more efficient than aerobic training to improve adipokine levels in aging individuals [21], our results are not surprising. The fact that leptin decreased whereas adiponectin levels remained unchanged suggested that adiponectin did not respond as well as leptin levels to exercise. In fact, a previous study in overweight postmenopausal women showed that leptin levels tended to decrease ($P = .06$) whereas adiponectin levels remained unchanged with a 14-week training program [24]. Moreover, a higher body weight loss induced by the combination of exercise and caloric restriction decreased leptin levels without any changes in adiponectin concentration in obese postmenopausal women [7]. Hence, it seems that higher body weight loss is probably not the reason why adiponectin did not respond as well as leptin levels to exercise intervention. On the other hand, it is interesting to note that LAR, a recognized useful marker of insulin resistance [10], tended to decrease after the intervention in all postmenopausal women. This result supports the fact that exercise combined with placebo or phytoestrogens could be used as an insulin resistance preventive strategy.

On the other hand, according to previous studies, phytoestrogen supplementation did not seem to reduce leptin concentrations in postmenopausal women [17,36,37]. Furthermore, previous studies from our laboratory [26] as well as others [38] have found that phytoestrogen supplementation may not be sufficient to decrease CRP concentrations and thus systemic inflammation in postmenopausal women. Finally, Llaneza et al [18] did not observe a synergic effect of aerobic exercise and a calorie-restricted diet combined with phytoestrogens on plasma leptin and CRP levels in obese postmenopausal women. Therefore, the fact that phytoestrogens did not add to the effect of exercise on leptin and CRP levels is in accordance with these studies.

It was previously reported that leptin and adiponectin are both involved in insulin sensitivity [39]. Our results showed that leptin was positively associated with plasma insulin and HOMA-IR at baseline and thus likely involved in insulin sensitivity. Furthermore, LAR was also positively associated with fasting glucose and insulin, as well as HOMA-IR and FM at baseline. These results support the fact that LAR is a better marker of insulin resistance than leptin alone in obese, nondiabetic, postmenopausal women, which is in good accordance with the literature [10]. Nevertheless, adiponectin did not present any association with FM and insulin level but had a negative relationship with CRP levels, which is in agreement with its anti-inflammatory role [40]. Because CRP was already associated with insulin resistance in postmenopausal women [41], our results suggest that leptin and adiponectin could both influence insulin sensitivity, but through different pathways. Moreover, a further study with a larger cohort could allow us to determine if adipokines and inflammation could be used instead of or with the classic metabolic disease risk factors.

According to our regression analyses, a higher HOMA-IR score and thus higher insulin resistance degree at baseline were associated with greater decrease in leptin level in response to mixed training. Because hyperleptinemia is associated with a higher risk of cardiovascular disease [9], this is interesting, as postmenopausal women with higher insulin resistance might thus greatly improve their chronic disease risk profile. Furthermore, greater decrease in plasma CRP occurred in subjects with higher fasting glucose and lower plasma adiponectin at baseline. These findings support the fact that postmenopausal women at higher risk of chronic diseases and type 2 diabetes mellitus [7,8,41] might greatly benefit from initiating an active lifestyle. Hence, although all postmenopausal women have benefited from the mixed training, these results may indicate that mixed exercise program could have a beneficial impact in obese postmenopausal women, especially those with a higher risk of chronic disease.

Our results also showed a slight increase in plasma glucose in all women after training alone or combined with phytoestrogens. Nevertheless, it should be noted that this increase was probably not clinically significant because it was less than 5% (0.20 mmol/L) and remained in the range of normal values in addition to being very comparable to a daily variation in fasting glucose [42]. It could also be hypothesized that FM changes were not yet stabilized in postmenopausal women. In fact, because of exercise-related increased adipose tissue lipolysis, it is possible that free fatty acids were more present in the bloodstream. Knowing that free fatty acids compete with glucose for mitochondrial oxidation (the Randle cycle), a potential increase in adipose tissue lipolysis could lead to a transitory slight increase in fasting glucose level. Nonetheless, without measures of adipose tissue lipolysis, we cannot confirm this hypothesis.

Some limits of this study may deserve attention. First, some variables did not have a normal distribution at baseline. Thus, we had to rely partly on nonparametric analyses. Second, we did not have a control group who did not perform exercise training and thus could not truly assess the sole impact of exercise. Finally, we did not have available serum to measure other inflammatory markers such as tumor necrosis factor–α, interleukin-6, or their receptors.

To our knowledge, this is the first randomized study to examine the combination of exercise training with phytoestrogens on adipokines and systemic inflammation. Although our results indicate that phytoestrogens and mixed exercise program do not additionally impact on these markers, they support that mixed training improves systemic inflammation and leptin concentrations in overweight to obese postmenopausal women. A further study with a larger sample size could allow us to verify if overweight and obese postmenopausal women similarly respond to a mixed exercise training combined with phytoestrogens. Our study supports the fact that mixed exercise training is an effective and accessible strategy to reduce some chronic disease factors and could thus be prescribed by kinesiologists as a preventive treatment in healthy aging women. Regarding the combination with phytoestrogens, our results showed that this strategy is not optimal, indicating that physicians should probably consider exercise alone rather than combined with phytoestrogens for chronic disease prevention in overweight but healthy postmenopausal women.

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Conflict of Interest

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

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