

Impact of weight loss with or without exercise on abdominal fat and insulin resistance in obese individuals: a randomised clinical trial

Ana Paula Trussardi Fayh^{1,2*}, André Luiz Lopes³, Pablo Rober Fernandes³, Alvaro Reischak-Oliveira³ and Rogério Friedman¹

¹Endocrine Unit, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

²Health Sciences College of Trairi, Universidade Federal do Rio Grande do Norte, Rua Vila Trairi S/N, Centro, Santa Cruz, RN 59200-000, Brazil

³Exercise Research Laboratory, School of Physical Education, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

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Abstract

Evidence supports an important contribution of abdominal obesity and inflammation to the development of insulin resistance (IR) and CVD. Weight loss in obese individuals can reduce inflammation and, consequently, IR, but the role of training remains unclear. The aim of this study was to evaluate the effects of body weight reduction with and without exercise over abdominal fat tissue (primary outcome) and IR. In this randomised clinical trial, forty-eight obese individuals (age 31.8 (SD 6.0) years, BMI 34.8 (SD 2.7) kg/m²) were randomised to either a diet-only group (DI) or a diet and exercise group (DI + EXE). Treatment was maintained until 5% of the initial body weight was lost. At baseline and upon completion, the following parameters were analysed: biochemical parameters such as glycaemia and insulin for the determination of homeostasis model assessment of insulin resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP) and abdominal computed tomography for the determination of visceral and subcutaneous adipose tissue. A total of thirteen individuals dropped out before completing the weight-loss intervention and did not repeat the tests. In both the DI (*n* 18) and DI + EXE (*n* 17) groups, we observed significant and similar decreases of visceral adipose tissue (difference between means: 7.9 (95% CI –9.5, 25.2) cm², *P* = 0.36), hs-CRP (difference between means: –0.06 (95% CI –0.19, 0.03) mg/l, *P* = 0.39) and HOMA (difference between means: –0.04 (95% CI –0.17, 0.08), *P* = 0.53). In the present study, 5% weight loss reduced abdominal fat and IR in obese individuals and exercise did not add to the effect of weight loss on the outcome variables.

Key words: Weight loss; Diet; Physical training; Obese; Insulin resistance

Evidence points to an important association of abdominal obesity with metabolic disease and CVD⁽¹⁾; hypertension, diabetes mellitus and clinical atherosclerotic disease are fairly common^(2–4), affecting the quality of life.

Abdominal fat is the sum of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in the abdominal region. VAT holds the highest association with the development of CVD and is related to insulin resistance (IR) and the secretion of pro-inflammatory cytokines⁽⁵⁾. Some of the products secreted in the adipose tissue, such as NEFA, TNF- α and IL-6, are strong stimuli for the production of high-sensitive C-reactive protein (hs-CRP) by the liver. C-reactive protein is a biomarker of low-grade inflammation; it is associated with a few comorbidities of obesity and has been regarded as a risk predictor for coronary artery disease⁽⁶⁾.

In clinical practice, anthropometric measures are used to estimate abdominal fat and to indirectly estimate the cardiovascular risk. The waist circumference (WC) and the waist:hip ratio are most widely recommended. However, they do not differentiate VAT from SAT. Furthermore, their clinical importance seems to be less significant in obese individuals⁽⁷⁾. Measuring VAT accurately is an important issue in the setting of obesity, if one wishes to detect changes in this metabolically active tissue. Among the existing imaging techniques, computed tomography of the abdomen is the 'gold standard' for measuring VAT⁽⁵⁾.

An intentional reduction of body weight by energy restriction reduces systemic inflammatory markers⁽⁸⁾ and improves IR⁽⁹⁾. In overweight patients, a reduction of 7% of the initial body weight improves systolic blood pressure, plasma glucose

Abbreviations: DI, diet-only group; DI + EXE, diet and exercise group; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IR, insulin resistance; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WC, waist circumference.

* **Corresponding author:** Dr. A. P. Trussardi Fayh, email apfayh@yahoo.com.br

and insulin⁽¹⁰⁾. Physical training can also be associated with lower levels of inflammation, and this has been attributed to its ability to contribute to the reduction of abdominal obesity and IR^(6,11). Individuals with the metabolic syndrome who are highly physically active have a lower concentration of hs-CRP than their sedentary counterparts⁽¹²⁾. Recent studies have explored the behaviour of inflammatory parameters and IR after physical training, but the results are still contradictory^(6,13). Thus, the aim of the present study was to compare the behaviour of hs-CRP, IR and VAT in obese patients who lose weight through diet therapy alone or diet combined with physical training.

Subjects and methods

Design and subjects

This is a randomised clinical trial involving obese adults (BMI 30 to 39.9 kg/m²), of both sexes, aged between 22 and 41 years, previously sedentary and without the use of drugs. Invitations to volunteers were advertised in newspapers, radio and television. Active smokers and patients with overt hypothyroidism, diabetes mellitus, grade III obesity, arterial hypertension, anaemia, active infection or cancer were excluded. The present study was conducted in accordance with the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre (08-282). Written informed consent was obtained from all subjects. The trial has been registered at ClinicalTrials.gov (NCT00929890; <http://clinicaltrials.gov>).

Procedures

Logistics. On admission to the study, we assessed anthropometric parameters, aerobic capacity, biochemistry and abdominal fat. A complete food history provided the parameters for the calculation of individual diets.

After these evaluations, the patients were allocated randomly to receive two different interventions: dietary counselling for weight reduction (DI) or dietary counselling for weight reduction accompanied by physical training (DI + EXE). The intervention was continued until the patients had lost 5% of their initial body weight. During the follow-up, patients had several outpatient visits where adherence to the diet was checked and stimulated.

When the 5% weight loss was reached, the baseline assessments were repeated.

Intervention. The diet plan was individually calculated to provide a reduction of between 500 and 1000 kcal (2090 and 4180 kJ) of energy intake per d. The prescribed diet was balanced and rich in fibre, according to current Brazilian guidelines for the treatment of obesity⁽¹⁴⁾. Every 2 weeks, we measured body weight and WC, and if necessary, adjustments were made to the diet to improve compliance.

The DI group received recommendations for light, informal physical activity, aimed at maintaining a healthy lifestyle⁽¹⁴⁾. In the outpatient visits, the practice of physical activity was

always stimulated. The subjects were encouraged to increase leisure-time physical activities, such as walking and dancing, avoiding high-intensity and long-duration exercises. A frequency of at least three times a week and a minimum duration of 30 min were systematically recommended.

The DI + EXE group was enrolled in a training programme. Three times a week, the participants attended the University gymnasium where they were supervised while training on a stationary bicycle, according to the following programme. In the first week of the training programme, subjects exercised for 30 min at an intensity of 50% of the heart rate reserve⁽¹⁵⁾. In the second week, the training time was 40 min per session, at an intensity of 60% of the heart rate reserve. From the third week onwards, subjects exercised at the target intensity, 70% of the heart rate reserve, for 45 min.

Measurements

Aerobic power. To determine the intensity of exercise, aerobic power was assessed by means of a protocol in cycle ergometer (Cybex). This consisted of a warm-up period of 3 min with a load of 25 W, followed by lifting the load a further 25 W/min until exhaustion. The heart rate was monitored by a heart rate monitor (Polar S810 HRM; Polar Electro Oy) and O₂ consumption and CO₂ production were measured using the CPX-D System (Medical Graphics) during the test. The maximum O₂ consumption was measured at maximal exercise, defined as the inability to continue exercising despite vigorous encouragement and confirmed by RER > 1.1, heart rate > 95% of maximum predicted for age and presence of plateau O₂ consumption even with increased load⁽¹⁶⁾.

Abdominal fat. To assess abdominal fat, anthropometric techniques and abdominal computed tomography were used.

Anthropometric measurements were body mass, height, WC and hip circumference, to calculate the waist:hip ratio.

Height was measured with a fixed stadiometer (Tonelli; Ltda), with a 1 mm precision. Body weight was measured on a digital scale (MEA-03 200; Plenna) in light indoor clothes, without shoes. WC was measured with an inelastic tape measure (Sanny), halfway between the last rib and the iliac crest. The nutritional status was classified by BMI (kg/m²)⁽¹⁷⁾.

Computed tomography (Philips Brilliance CT) was used for the determination of abdominal adipose tissue from a single tomographic slice at the L4–L5 level, as described by Seidell *et al.*⁽¹⁸⁾. To define the VAT (cm²), a continuous line was drawn by an electronic cursor, along the fascia transversalis and along the fascia of the quadratus lumborum muscle, excluding the vertebral body. In the area so defined, retroperitoneal, mesenteric and omental fat was included. The total abdominal adipose tissue area was measured in a similar way, but the line was drawn over the outer limits of the tomographic image of the abdominal wall⁽¹⁸⁾. SAT was calculated by subtracting VAT from the total abdominal adipose tissue. All examinations were carried out by a single, blinded technician.

Biochemical measurements. Venous blood samples were obtained after an overnight fast. The hs-CRP was determined by nephelometry (Boehringer), plasma glucose

by a glucose-peroxidase automated method (Advia; Bayer), plasma insulin by electrochemiluminescence (Elecsys; Roche) and uric acid by a colorimetric enzymatic method (Advia; Bayer). IR was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR), as proposed by Matthews *et al.*⁽¹⁹⁾:

$$\text{HOMA-IR} = \frac{\text{fasting insulin } (\mu\text{IU/ml}) \times \text{fasting glucose (mmol/l)}}{22.5}$$

Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows, version 19.0 (IBM). All variables were examined for normality of the distribution by the Kolmogorov–Smirnov test. Because of non-symmetrical distributions, HOMA-IR and hs-CRP were log-transformed for the statistical analyses. Nevertheless, for the sake of clarity, values are presented in the original scale. Data are presented as means and standard deviations or medians and interquartile ranges, and 95% CI. Descriptive statistics were used to identify sample characteristics and provide summary indices of selected measures. Baseline demographic and clinical characteristics were compared using either ANOVA or the Kruskal–Wallis test for continuous

variables and the χ^2 test for categorical variables. Changes in outcomes were analysed by general linear model for repeated measurements, with measurements at different interventions as a within-subjects factor. A one-way ANCOVA, using the baseline measurements as the covariates, was conducted to evaluate differences between DI and DI + EXE. Results were considered significant if the *P* value was <0.05.

Results

Fig. 1 shows the flow diagram of patient recruitment and randomisation. In total, forty-eight subjects performed all baseline assessments, eight men in each group. After performing the initial assessments, thirteen subjects dropped out (two men and four women of the DI group and one man and six women of the DI + EXE group). At baseline, the subjects who dropped out did not differ significantly from those who completed the study (*P*>0.05 for all variables). Even after exclusion of dropouts, the groups did not show statistically significant differences in baseline values (*P*>0.05 for all).

Adherence to training, which was assessed by attendance at exercise sessions and permanence on the target intensity, was above 85% for all participants. The time required for the reduction of 5% of the initial body weight was 79.7

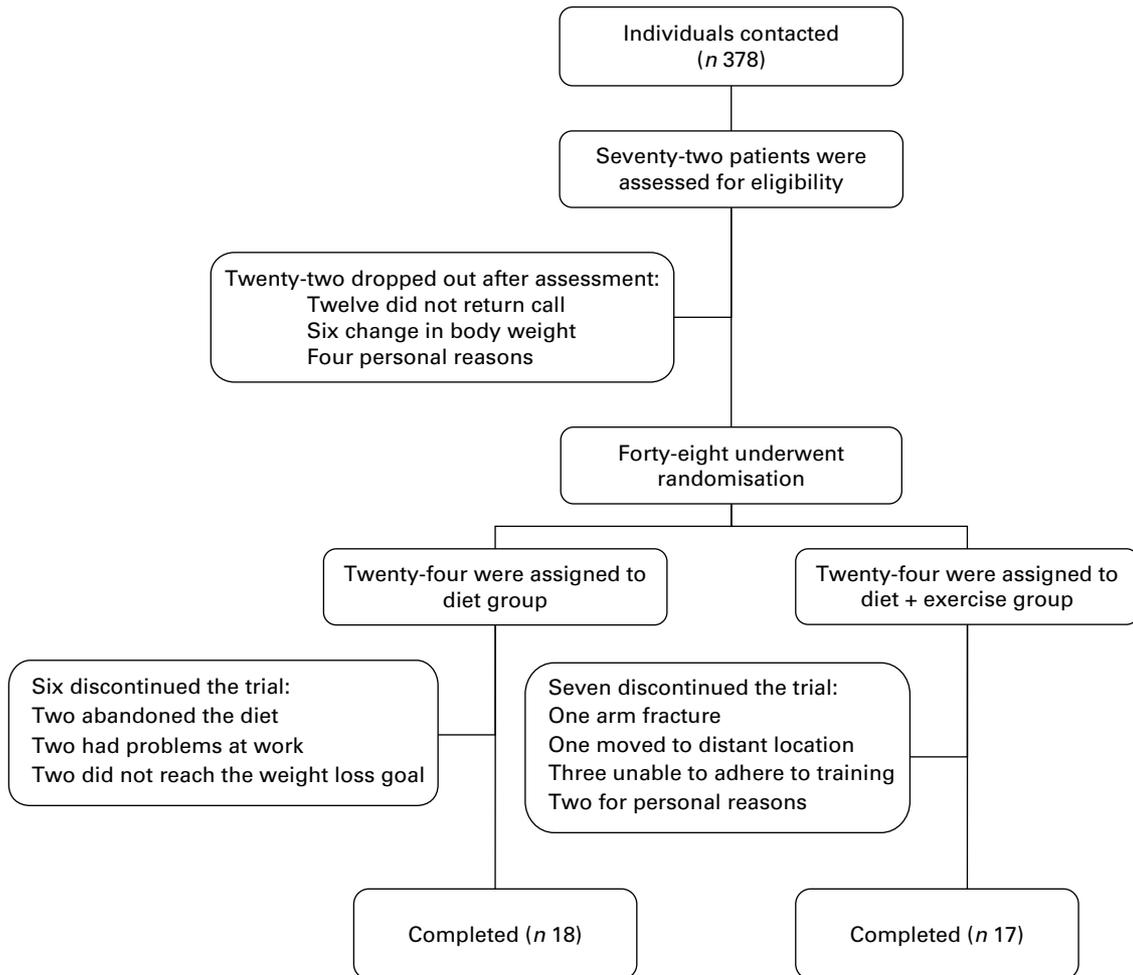


Fig. 1. Flow diagram of patient recruitment and randomisation.

Table 1. Anthropometric and biochemical changes with different interventions
(Mean values and standard deviations; medians and interquartile ranges (IQR))

	DI (n 18)				DI + EXE (n 17)				P*	Mean difference between groups	95 % CI		P†
	Before		After		Before		After				Lower	Upper	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD					
Age (years)	30.1	5.5	–	–	32.4	7.0	–	–	–	–	–	–	–
Body weight (kg)	95.8	13.7	91.5	14.2	98.7	13.0	94.0	13.0	0.00	0.35	– 1.13	1.83	0.63
VO _{2max} (ml/kg per min)	24.5	4.3	25.2	4.4	25.1	4.9	27.6	5.2	0.04	1.8	0.35	2.8	0.02
BMI (kg/m ²)	34.7	2.4	33.1	2.6	34.7	2.4	33.1	2.7	0.00	0.01	– 0.02	0.02	0.79
Waist circumference (cm)	112.0	8.7	108.3	8.7	110.9	7.4	107.0	7.8	0.00	0.20	– 1.08	1.47	0.76
Hip circumference (cm)	120.4	8.8	117.1	8.6	120.2	5.1	117.0	4.7	0.00	– 0.12	– 1.29	1.06	0.84
Waist:hip ratio	0.83	0.09	0.83	0.09	0.86	0.08	0.85	0.07	0.06	0.01	– 0.01	0.02	0.09
Glycaemia (mg/l)	924	92	897	92	904	97	904	68	0.42	– 27.2	– 60.4	5.9	0.59
Insulin (μIU/ml)‡									0.01	– 0.03	– 0.15	0.08	0.56
Median		17.3		15.4		15.5		13.4					
IQR		14.7–21.6		7.8–19.6		11.4–18.7		8.8–19.8					
HOMA									0.01	– 0.04	– 0.17	0.08	0.53
Median		4.1		3.3		3.1		3.2					
IQR		3.1–5.6		1.7–4.3		2.5–4.7		2.0–4.4					
Uric acid (mg/l)	5.4	1.3	5.3	1.1	5.4	1.6	5.4	1.1	0.65	– 0.01	– 0.39	0.36	0.95
hs-CRP (mg/l)									0.01	– 0.06	– 0.19	0.08	0.39
Median		3.3		2.8		3.5		3.0					
IQR		2.4–6.4		1.5–4.8		1.5–5.8		1.1–5.9					

DI, diet-only group; DI + EXE, diet and exercise group; HOMA, homeostasis model assessment; hs-CRP, high-sensitivity C-reactive protein.

* P for intervention with general linear model for repeated measurements (before v. after).

† P with ANCOVA adjusted for baseline measures.

‡ 1 μIU/ml = 6.945 pmol/L.

Weight loss in obese individuals

(63–95) d for the DI group and 65.9 (55–76) d for the DI + EXE group. This difference was not statistically significant ($P=0.16$). In the DI group, an average daily energy deficit of 2457.3 (SD 565.7) kJ (587.3 (SD 135.2) kcal) was obtained with the energy intake restriction. In the DI + EXE group, an average daily energy deficit of 2980.7 (SD 739.7) kJ (712.4 (SD 176.8) kcal) was provided by energy restriction and exercise. This difference was statistically significant ($P=0.03$).

Table 1 shows the effect of interventions on anthropometric and biochemical parameters. Weight loss was accompanied by significant reductions in BMI, WC, hip circumference, insulin, HOMA and hs-CRP. These reductions were not different between the groups ($P>0.05$ ANCOVA). There were no changes in glycaemia or uric acid.

Fig. 2 shows the effect of the interventions on abdominal fat, evaluated by computed tomography. After a 5% body weight reduction, both groups reduced total abdominal

adipose tissue: in DI, from 660.3 (SD 137.1) to 608.5 (SD 147.5) cm^2 ($P=0.01$); in DI + EXE, from 622.8 (SD 128.5) to 576.9 (SD 137.2) cm^2 ($P=0.04$). The difference between the mean reductions in the groups was non-significant (-3.5 (95% CI $-52.2, 45.2$) cm^2 , $P=0.88$). VAT was also reduced: in DI, from 136.1 (SD 64) to 112.5 (SD 54) cm^2 ($P=0.01$) and in DI + EXE, from 154.23 (SD 60.6) to 118.80 (SD 55.36) cm^2 ($P=0.02$), with a non-significant difference between the mean reductions of 7.9 (95% CI $-9.5, 25.2$) cm^2 ($P=0.36$). Neither treatment significantly altered the SAT ($P>0.05$).

Discussion

In the present study, a 5% reduction in body weight was associated with a reduction in visceral fat, hs-CRP and IR in obese individuals. Previous studies have shown an improvement in insulin sensitivity and inflammatory parameters with this amount of weight loss in obese patients undergoing energy restriction of 2092–3347 kJ/d (500–800 kcal/d) without physical training^(10,20). However, other studies suggest that a significant improvement in these parameters would require a reduction of up to 4184 kJ/d (1000 kcal/d) by dietary restriction accompanied by increased energy expenditure through physical training^(21,22). The present results indicate that, at least in the short run, a modest weight loss, via energy restriction, with or without physical training, is associated with improvement in inflammatory parameters, VAT and IR. In the long run, increasing energy expenditure may be required.

VAT has greater cardiometabolic impact than SAT^(23,24). However, because SAT has a greater total mass, it can contribute to the relationship between central adiposity, IR and CVD⁽²⁵⁾. Few studies have investigated the effects of diet and exercise on these tissues and the impact on cardiovascular risk reduction. Marques *et al.*⁽²⁶⁾ suggest that VAT areas with values above 100 cm^2 increase the risk of metabolic complications such as raised plasma glucose, total cholesterol and blood pressure. When the VAT area exceeds 150 cm^2 , the risk of developing coronary artery disease increases about threefold⁽²⁶⁾. Kim *et al.*⁽⁶⁾ measured the abdominal fat of 160 middle-aged Korean adults, both eutrophic and overweight. The VAT average was 89.5 (SD 46.3) cm^2 , and men showed higher values than women. Our patients had baseline VAT of 141.6 (SD 62.1) cm^2 , suggesting a higher risk of metabolic complications, corroborated by IR and elevated hs-CRP. IR and the accompanying high fasting plasma insulin are frequently found in obese individuals and appear to be the first signs of the future development of type 2 diabetes^(13,27).

Exercise is associated with reduced cardiovascular risk, especially in individuals with diabetes, improving endothelial function and inflammatory markers^(28,29). The effects of exercise on the markers of inflammation may be more pronounced in individuals with features of the metabolic syndrome when compared with those without metabolic abnormalities⁽¹²⁾. We did not find a significant additional effect of exercise training on the markers of inflammation or IR. In women who lose weight through diet, hs-CRP, TNF- α and IL-6 are reduced in a similar fashion in those exercising or not⁽³⁰⁾. In a randomised

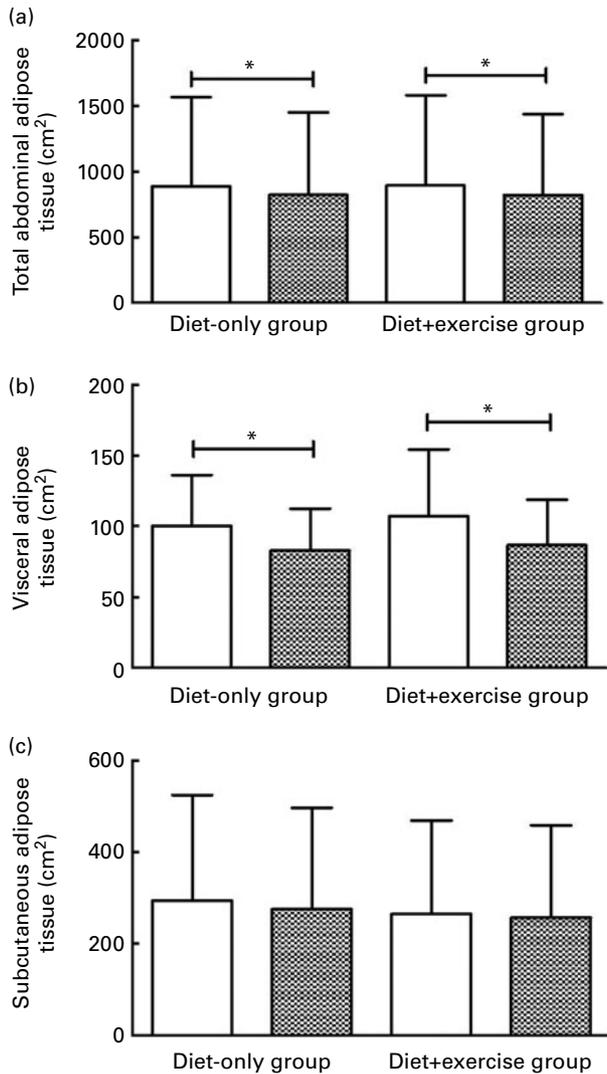


Fig. 2. Effect of interventions on (a) total abdominal adipose tissue, (b) visceral adipose tissue and (c) subcutaneous adipose tissue evaluated by computed tomography. Values are means and standard deviations represented by vertical bars. * $P < 0.05$ for intervention with general linear model for repeated measurements (before (□) v. after (■)).

clinical trial with older obese adults, hs-CRP was significantly lowered in the subjects on a diet only⁽²⁰⁾. It is possible that the length of exposure to exercise was not enough to promote cardiovascular protection. Alternatively, the acute generation of free radicals induced by acute exercise could have contributed to these findings^(20,31). Speculatively, the relatively short time period between the last exercise session and the final biochemical analyses of the studies could have contributed to the findings^(20,31). The amount of exercise might not have been enough to elicit the antioxidant protection of physical training⁽³¹⁾. It is therefore likely that the process of ischaemia–reperfusion of aerobic exercise caused a rapid increase in blood flow (reperfusion) and the generation of free radicals⁽³²⁾.

Previous studies suggest that the levels of hs-CRP may bear an important association with variations in insulin sensitivity^(33,34). In obese but otherwise metabolically healthy individuals, low levels of hs-CRP may contribute to the favourable glucose profile, even with increased body adiposity⁽³⁵⁾. Our patients had a relatively benign glucose profile, but somewhat elevated hs-CRP. This could have had an impact on the results, minimising effects that could otherwise be significant in those patients with more evident metabolic disturbances.

In the present study, losing weight was associated with improved insulin levels and HOMA, but exercise did not contribute to additional improvement. Oberbach *et al.*⁽¹³⁾ did not find significant reductions in glucose and insulin concentrations in twenty subjects with normal glucose tolerance after 4 weeks of aerobic training. The training programme adopted by the authors was shorter than ours and involved a concurrent training (aerobic + resistance), while our protocol was just aerobic. Although further exploration is much needed, such results suggest that different exercise regimens can bring different effects on these parameters.

Physical activity increases energy requirements and therefore assists in weight loss by contributing to higher daily energy expenditure. In this sample, although the subjects who did exercise training increased their aerobic capacity, no additional benefits in other metabolic parameters were found. One possible explanation for this finding is the low energy expenditure caused by exercise sessions. The traditional recommendation of at least 150 min/week of exercise⁽³⁶⁾ was not met with the programme proposed in this protocol. Training alone produced a weekly energy deficit of 875.7 (SD 215.2) kcal in the DI + EXE subjects, matching the recommendations of weekly energy expenditure for the prevention of chronic diseases, but falling short of the recommended energy deficit for weight loss⁽³⁷⁾. Probably, the total exercise load was insufficient to promote additional physiological benefits for this group of patients who were free of metabolic diseases other than obesity.

The strength of the present study was the use of the same percentage weight-loss goal for all subjects, in order to evaluate eventual differential effects of the inclusion of physical training in the therapeutic regimen. If the design were based on a fixed duration of treatment, the results in terms of weight loss and body composition change might have been different in the two groups. Interestingly, the time needed to achieve the 5% goal was not different in the two regimens.

The use of computer imaging techniques for the evaluation of abdominal fat distribution gave the study more power to accurately identify the effect of weight loss in different types of adipose tissue.

The limitation of the present study was the absence of a control group (similar follow-up without weight loss, with or without physical training). However, it was considered unethical to treat a group of obese individuals without stimulating them to lose weight during any given period of time. With this design, we believe that it was possible to test the hypothesis of a differential effect of exercise on several parameters. Since the results are negative, one cannot avoid looking into issues such as sample size and duration of the interventions. In the present study, the power was 80% to detect a difference with effect size ≥ 1 . Although the sample size was initially estimated to detect differences in the 5% significance area, a larger sample might have led to different findings. This will have to be clarified in further studies.

Conclusion

A reduction of 5% of the initial body weight resulted in significant decreases in VAT and total abdominal adipose tissue in obese individuals, the primary outcome of the present study. Additionally, this weight loss decreased HOMA-IR and hs-CRP. Exercise did not add any measurable benefit in as far as the variables in the present study are considered.

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