Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients

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ABSTRACT

Background. The prevalence of obesity has markedly increased in patients with chronic kidney disease (CKD). Studies on the impact of exercise focusing on obese CKD patients are scarce. Therefore, we aimed to investigate the effect of aerobic exercise performed either in an exercise centre or at home on visceral fat in overweight non-dialysed CKD patients.

Methods. Twenty-seven sedentary men (52.1 ± 9.5 years, body mass index 30.4 ± 3.8 kg/m², estimated glomerular filtration rate (eGFR) 27.5 ± 11.6 mL/min) were randomly assigned to a centre-based exercise group (n = 10), home-based exercise group (n = 8) or control group (n = 9). The aerobic training was prescribed according to ventilatory threshold and performed three times per week during 12 weeks. Body composition was assessed by dual energy X-ray absorptiometry (DEXA) and the distribution of abdominal fat by computed tomography.

Results. In the centre-based group, visceral fat and waist circumference decreased 6.4 ± 6.4 mm (P < 0.01) and 2.0 ± 2.3 cm (P = 0.03) and leg lean mass increased 0.5 ± 0.4 kg (P < 0.01). No significant changes were observed in the home-based group. Visceral fat increased 5.0 ± 4.4 mm in the control group (P = 0.01). In relation to the control, a group-by-time interaction was significant for visceral fat and waist circumference for both exercise groups and for leg lean mass for the centre-based group. Mean blood pressure decreased in both exercise groups (centre-based 13%, P < 0.01 and home-based 10%, P = 0.03) and eGFR increased 3.6 ± 4.6 mL/min (P = 0.03) in the centre-based group. These parameters remained unchanged in the control group.

Conclusions. Centre-based aerobic exercise is an effective approach to reduce visceral fat besides promoting relevant clinical benefits in male overweight CKD patients.

Keywords: aerobic exercise, chronic kidney disease, visceral fat

INTRODUCTION

Obesity has become a worldwide epidemic with growing prevalence across all age groups around the world. Obesity is a well-documented risk factor for diabetes and hypertension, the two primary causes of chronic kidney disease (CKD) [1, 2]. Moreover, obesity may itself be an independent risk factor for the development and progression of CKD [3, 4]. Excess of abdominal fat, especially visceral fat, has shown to be associated with cardiovascular risk factors [5, 6]. The predictive power of increased abdominal fat on cardiovascular events and mortality has been demonstrated in the early stages of CKD [7, 8].

Lifestyle change, including dietary restriction and physical exercise, is the recommended management for obesity in the general population. Although those approaches could be extended to obese patients with CKD, some peculiarities related to the disease treatment may render the implementation of such interventions difficult. Several specific dietary modifications are already part of the treatment of CKD patients. Thus, additional restrictions such as in energy intake could
impair compliance besides being a potential risk factor for protein-energy wasting. In regards to the physical exercise, several factors such as the disease per se, reduced physical capacity, fear of adverse events, lack of place and equipment and lack of knowledge of the benefits limit the incorporation of exercise into treatment plans. In the last years, an increasing number of reports have emerged testing the benefits of exercise on physical function capacity but few have investigated the effect of exercise on body composition of obese CKD patients. Only two studies tested the impact of aerobic exercise on body composition in non-dialysed CKD patients. A pilot study with 13 obese diabetic patients with CKD showed no changes in body weight or body composition after 24 weeks of a walking programme [9]. In the study by Kosmadakis et al.[10] with non-dialysed CKD patients a walking programme resulted in a reduction of total fat mass and a trend to increase lean body mass (LBM) after 4 weeks of training, but this benefit was not maintained after 24 weeks. The impact of exercise on body composition is still unclear and deserves further investigation. Hence, in the present study, we aimed to investigate in a sample of overweight CKD patients the effect of aerobic exercise on parameters of body composition with special focus on visceral fat. In addition, as a secondary aim, we tested the effects of a home-based exercise mode in comparison to that of a centre-based exercise.

MATERIALS AND METHODS

Subjects

Twenty-nine sedentary men with CKD stages 3 and 4 were recruited from the outpatient clinic of the Federal University of São Paulo–Oswaldo Ramos Foundation (São Paulo, SP, Brazil) (Figure 1). The inclusion criteria were body mass index (BMI) > 25 kg/m², age between 18 and 70 years, and systolic and diastolic blood pressure < 180 and < 100 mmHg, respectively, serum haemoglobin > 11 g/dL, glycated haemoglobin (HbA1c) < 8%, and absence of chronic obstructive pulmonary disease, congestive heart failure or active coronary disease. Patients who used beta blockers or erythropoietin or with a positive cardiovascular stress test were not included. As part of the nutritional routine care in our centre, a renal-specific diet containing 25–30 kcal/adjusted body weight/day and 0.6–0.8 g/adjusted body weight/day of protein was prescribed to all patients, and no modification was performed during the study. Patients were taking antihypertensive drugs, diuretics, lipid lowering medication, uric acid medication and oral antidiabetics. No medication modification was done during the follow-up. The Human Investigation Review Committee of Federal University of São Paulo approved the study, and informed consent was obtained from each subject.

Study protocol

This was a prospective, randomized, controlled interventional trial of 12 weeks. Patients were randomized to aerobic exercise group \( (n = 19) \) or control group \( (n = 10) \). Those assigned to the aerobic exercise group chose the exercise mode as centre-based \( (n = 10) \) or home-based \( (n = 9) \). One patient in the control group was excluded after 6 weeks of follow-up due to a diagnosis of colon cancer and one patient in the home-based withdrew (Figure 1). The patients from the centre-based exercise group performed the aerobic training on a treadmill three times per week during 12 weeks on alternate days at the Psychobiology and Exercise Study Centre under supervision of an exercise physiologist. The patients from the home-based exercise group performed aerobic training at locations nearby their home, backyard, park or street three times per week on alternate days during 12 weeks according to the instructions

given by exercise physiologist. In order to correctly perform the exercise, the home-based patients were initially submitted to three supervised exercise sessions and then were monitored weekly by telephone calls and in monthly visits to assess progress, adherence and to provide support. The patients from the control group were advised not to perform any type of physical exercise during follow-up. Physical and functional capacities, body composition, blood pressure and laboratory parameters were assessed at baseline and after 12 weeks.

**Aerobic training**

The exercise intensity was prescribed according to ventilatory threshold (VT) obtained in the cardiopulmonary exercise test. The VT is characterized by the highest intensity of physical exertion fully maintained by aerobic energy pathways, and is considered a marker of exercise consistent with mild to moderate intensity and is usually found to be between 40 and 60% maximum VO2 [11, 12]. The intensity control was done by means of the heart rate value obtained at VT. Each patient from the home-based exercise group received a heart rate monitor to control exercise intensity (Polar FS1, Polar Electro Oy, Finland). The training programme was conducted in accordance with the recommendations of the American College of Sports Medicine [13]. All training sessions were preceded by stretching of the large muscle groups and warm up (5 min) and ended by cooling down and stretching (5 min) for the centre-based exercise group, and the same advice was given to the home-based exercise group. The aerobic training was performed for 30 min with increment of 10 min in duration every 4 weeks during 12 weeks. For the home-based exercise group, the adjustment of the load of exercise was performed monthly during a supervised training session.

**Physical and functional capacity evaluation**

Physical capacity was determined by cardiopulmonary exercise test on a treadmill. The test began with a fixed inclination of 1%. The initial velocity was 2 km/h during the first 3 min with increments of 0.5 km/h every minute until the patient reached physical exhaustion. The VO2peak was measured using a gas analyser (Quark PFT Cosmed 4, Rome, Italy), and was collected by the method of breath by breath. The highest VO2 obtained during the last stage reached was considered the VO2peak. The speed in VO2peak was the highest speed obtained during the last stage. Functional capacity was assessed by 6-min walk test (maximal distance walked along an internal corridor during 6 min) and sit-to-stand test (maximal sit to stand cycles achieved in 30 s).

**Abdominal computed tomography**

Visceral fat and subcutaneous fat were obtained by using computed tomography (Brilliance CT 16-slice; Philips, Cleveland, OH, USA). Patients were examined in the supine position with both arms stretched above the head, and slices of 10 mm scan were measured at the level of the umbilicus (approximately the L4–L5 intervertebral space). Visceral fat was determined by measuring the distance between the aortic artery and abdominal musculature. Subcutaneous fat was determined by measuring the distance between the abdominal wall to the subcutaneous tissue. The values of linear measurement are shown in millimetres. The same blinded skilled technician performed all measurements during the study.

**Dual energy X-ray absorptiometry**

Fat mass and LBM were measured using a scanner DPX model (Lunar Radiation Corporation, Madison, WI, USA). Each patient underwent standard soft-tissue examination including whole-body and regional measurements of trunk, arms and legs.

**Anthropometry and dietary intake**

BMI was calculated as body weight divided by squared height. Adjusted body weight was calculated according to an equation recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative [14]. Waist circumference was measured at the umbilicus level at the end of expiration using a flexible plastic tape. The mean of three measurements was used for analysis. Energy intake was estimated by using a 3-day food record.

**Laboratory data**

Blood samples were drawn after an overnight fast of at least 12 h. Serum creatinine, albumin (brom cresol green), haemoglobin and high-sensitivity C-reactive protein (immunoluminescence) were determined. Serum glucose and insulin (immunofluorometric assay) were measured in order to calculate the homeostatic model assessment (HOMA) index [15]. Glomerular filtration rate (GFR) was estimated by the using the CKD–EPI creatinine equation [16]. Twenty-four-hour urine was collected to determine urinary sodium which was used as an estimation of sodium intake.

**Mean blood pressure**

Blood pressure was assessed with the patient in a sitting position after 10 min rest. During the evaluation week, the average of three readings performed on alternate days was used to calculate mean blood pressure. The mean blood pressure was calculated as: diastolic blood pressure + [systolic blood pressure – diastolic blood pressure] ÷ 3.

**Statistical analysis**

The sample size was calculated considering a mean of 5% reduction of visceral fat within group [17]. On the basis of repeated-measures analysis of variance, a total of eight patients for each group were calculated to ensure a power of 80% and P-value of < 0.05.

Data are presented as mean and standard deviation, median and interquartile or proportions on the basis of the distribution of the variables. Skewed variables were log-transformed. Three-way analysis of variance (ANOVA) was initially performed to identify whether or not there were differences among the three groups. Two-way ANOVA was employed for between-group comparisons and to determine group-by-time interaction. ANOVA for repeated measures was used to compare variables within the groups. The χ² test was used for comparisons of proportions among the groups. All tests were two sided, and statistical significance for all analyses was established at P values of 0.05.
Twenty-seven patients completed the 12-week follow-up. The main causes of CKD were hypertensive nephrosclerosis (40.8%), chronic glomerulonephritis (22.2%), diabetic nephropathy (7.4%), undetermined (14.8%) and others (14.8%).

Table 1 shows the baseline and follow-up comparison among the centre-based exercise group, home-based exercise group and control group. No significant differences for any variables were identified among the groups at baseline.

**RESULTS**

Centre-based exercise group versus control group

Repeated measures analysis of variance revealed significant group-by-time interactions after exercise training for speed achieved at VO$_{2peak}$ and sit-to-stand test. These exercise capacity markers and 6-min walk test increased significantly in the centre-based group and did not change in the control. A significant group-by-time interaction was found for visceral fat, waist circumference, total body fat and leg lean mass. Visceral fat and waist circumference decreased in the centre-based group. In the control group, visceral fat increased significantly with no significant change in waist circumference. Figure 2 shows the percentage of changes of visceral fat and waist circumference after 12 weeks. As depicted in Table 1, LBM increased in the centre-based group due to the increase in the leg lean mass. Total body fat did not change within the groups but, since the pattern of changes was different between the two groups, the interaction group by time was significant. No significant changes were seen in other nutritional parameters. A significant group-by-time interaction was observed for estimated glomerular filtration rate and mean blood pressure. Renal function and blood pressure improved in the centre-based group, while no changes were observed in the control group. The other laboratory parameters remained unchanged in both groups.

Home-based exercise group versus control group

Similar to the centre-based group, a significant group-by-time interaction was found for speed achieved at VO$_{2peak}$ and sit-to-stand test. These variables and 6-min walk test increased in the home-based group and did not change in control group. As can be seen in Table 1, no significant changes in body weight, BMI, visceral fat, waist circumference and total body fat were found in the home-based group. Except for waist circumference and total body fat, those nutritional markers increased in the control group during the 12-week follow-up. As a result, the group-by-time interaction was significant for those parameters. Mean blood pressure decreased in the home-based group and did not change in the control group. No significant group-by-time interaction was found for mean blood pressure or laboratory parameters.

No significant group-by-time interaction was found for any variable when comparing centre-based and home-based exercise groups.

**DISCUSSION**

In the present study, centre-based aerobic exercise resulted in a significant reduction of visceral fat of the non-dialysed CKD patients with excess of body weight. To the best of our knowledge, the present study is the first to show the impact of aerobic exercise as a single intervention on visceral fat reduction in obese CKD patients. We found that visceral fat decreased on average 6% among patients in the centre-based exercise group, ranging from 3 to 10%. These results are in accordance with studies including overweight patients with normal renal function in which the aerobic training programme was similar to that employed in our study. In the mentioned reports, the reduction of visceral fat varied from 5 to 13% [17–20]. It is important to remark that in those studies as well as in ours, a significant reduction of visceral fat was achieved even under mild-to-moderate intensity exercise.

Aerobic exercise induces a negative energy balance and consequently reduces fat mass, as long as there is no compensation in other components of energy expenditure or energy intake [21]. It has been suggested that visceral fat is used more quickly as an energy source than subcutaneous fat [22], and the degree of reduction could be directly attributed to the aerobic exercise intensity [23]. Since in the present study, the intensity of the exercise was mild to moderate and there was no change in the energy intake, the changes in energy balance were probably not sufficient to promote significant reductions in the total fat mass but enough to reduce visceral fat.

If, on the one hand, a positive effect on visceral fat was observed in the exercise group, on the other a negative finding was observed in the control group that experienced a significant increase in visceral fat. In accordance, a previous investigation of our group showed a spontaneous accumulation of visceral fat over a year in 70% of non-dialysed CKD patients [24]. This is of concern since there is evidence that increased visceral fat is associated with atherosclerosis, inflammation and insulin resistance in both haemodialysis [5, 6, 25] as well as in non-dialysed CKD patients [26]. Additionally, it has been recently demonstrated that visceral obesity was able to predict future cardiovascular events in non-dialysed CKD patients [7]. Therefore, therapeutic approaches to reduce the visceral fat compartment are undoubtedly warranted for the CKD population.

This study also demonstrated that waist circumference, a simple marker of abdominal obesity, was able to detect reduction in visceral fat. We have previously validated waist circumference as a marker of abdominal fat in non-dialysed CKD patients as well as in peritoneal dialysis patients in cross-sectional and prospective analyses [24, 26, 27]. Herein, we observed that waist circumference was able to mirror reduction of visceral fat in patients under centre-based exercise intervention. Therefore, waist circumference may be an alternative for monitoring abdominal fat in the routine practice of obese CKD patients.

Another important effect of the exercise on the patient’s body composition in the current study was the increase of LBM in the centre-based exercise group. This finding was somewhat unexpected since this is a benefit more commonly associated with resistance exercise [28–30] and not with aerobic training.
Table 1. Exercise parameters, body composition, energy intake and laboratory markers at baseline and after 12 weeks

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Centre-based exercise group (n = 10)</th>
<th>Home-based exercise group (n = 8)</th>
<th>Control group (n = 9)</th>
<th>Group-by-time interaction</th>
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<tr>
<td></td>
<td>Baseline 12 weeks</td>
<td>P</td>
<td>Baseline 12 weeks</td>
<td>P</td>
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<tr>
<td><strong>Exercise parameters</strong></td>
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<tr>
<td>VO_{peak} (mL/kg/min)</td>
<td>24.8 ± 4.5</td>
<td>– NA</td>
<td>27.8 ± 6.2</td>
<td>0.10</td>
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<tr>
<td>Speed in VO_{peak} (km/h)</td>
<td>7.5 ± 1.2</td>
<td>– &lt;0.01</td>
<td>8.6 ± 1.5</td>
<td>0.02</td>
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<tr>
<td>6-min walk test (m)</td>
<td>559.1 ± 85.4</td>
<td>– &lt;0.01</td>
<td>662.8 ± 88.4</td>
<td>&lt;0.01</td>
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<tr>
<td>Sit-to-stand test (repetition)</td>
<td>17.7 ± 3.9</td>
<td>– &lt;0.01</td>
<td>24.0 ± 5.3</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>Nutritional parameters</strong></td>
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<tr>
<td>Body weight (kg)</td>
<td>86.2 ± 19.4</td>
<td>– 0.60</td>
<td>86.1 ± 20.7</td>
<td>0.60</td>
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<tr>
<td>Body mass index (kg/m^2)</td>
<td>30.8 ± 5.1</td>
<td>– 0.75</td>
<td>30.7 ± 5.5</td>
<td>0.75</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>106.8 ± 16.7</td>
<td>– 0.03</td>
<td>104.9 ± 16.0</td>
<td>0.03</td>
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<tr>
<td>Subcutaneous fat (mm)</td>
<td>18.4 ± 7.7</td>
<td>– 0.94</td>
<td>18.3 ± 6.9</td>
<td>0.94</td>
</tr>
<tr>
<td>Total body fat (kg)</td>
<td>24.2 ± 5.1</td>
<td>– 0.18</td>
<td>23.4 ± 5.8</td>
<td>0.18</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>52.5 ± 5.4</td>
<td>– &lt;0.01</td>
<td>53.7 ± 5.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arm lean mass (kg)</td>
<td>6.8 ± 0.9</td>
<td>– 0.36</td>
<td>6.9 ± 1.0</td>
<td>0.36</td>
</tr>
<tr>
<td>Leg lean mass (kg)</td>
<td>18.0 ± 1.3</td>
<td>– 0.01</td>
<td>18.5 ± 1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Energy intake (kcal/kg/day)</td>
<td>21.6 ± 6.9</td>
<td>– 0.70</td>
<td>21.1 ± 6.4</td>
<td>0.70</td>
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<tr>
<td><strong>Laboratory and clinical data</strong></td>
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<tr>
<td>eGFR (mL/min/1.73 m^2)</td>
<td>25.8 ± 8.8</td>
<td>– 0.03</td>
<td>29.4 ± 8.7</td>
<td>0.03</td>
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<tr>
<td>Serum haemoglobin (g/dL)</td>
<td>13.9 ± 1.3</td>
<td>– 0.48</td>
<td>13.8 ± 1.4</td>
<td>0.48</td>
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<tr>
<td>Serum albumin (g/dL)</td>
<td>4.4 ± 0.2</td>
<td>– 0.20</td>
<td>4.3 ± 0.2</td>
<td>0.20</td>
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<td>Urinary sodium (mEq/24 h)</td>
<td>224 (174–277)</td>
<td>– &lt;0.01</td>
<td>272 (212–310)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HOMA index</td>
<td>2.9 (2.1–4.5)</td>
<td>– 0.80</td>
<td>2.9 (2.0–4.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>0.26 (0.11–2.20)</td>
<td>– 0.37</td>
<td>0.22 (0.14–0.48)</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>97.7 ± 7.4</td>
<td>– &lt;0.01</td>
<td>84.7 ± 5.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation or median and interquartile range.

eGFR, estimated glomerular filtration rate; HOMA, homeostatic model assessment; NA, not applicable.

\(^a\) Group-by-time interaction between centre-based exercise group versus control group.

\(^b\) Group-by-time interaction between home-based exercise group versus control group.

\(^c\) Group-by-time interaction between centre-based exercise group versus home-based exercise group.
In general, the influence of aerobic exercise on skeletal muscle mass and function has been poorly understood and studies have reported conflicting data. While some researchers have shown significant muscle hypertrophy in elderly and in haemodialysis patients as a result of aerobic exercise [31, 32], others did not observe any change in LBM [33, 34]. Differences in the exercise programme characteristics, methods of determining LBM and study populations may account for the heterogeneous findings. The finding in the current study is relevant, since reduced LBM has been associated with poor outcomes in the CKD population [35]. Further studies are needed to better understand the effect of aerobic exercise on LBM of CKD patients.

The aerobic exercise in our study also resulted in a significant reduction of blood pressure of the patients. Such clinical benefit of exercise has been well established in normotensive and hypertensive individuals [36, 37] as well as in CKD patients [38]. Aerobic training lowers blood pressure by reducing peripheral vascular resistance due to the improvement of endothelium-mediated vasodilatation, attenuation of increased sympathetic nervous system activity and vascular remodelling [37]. It is of note that, in the present study, the blood pressure reduction occurred regardless of changes of body weight, sodium intake or use of antihypertensive medication, confirming the effect of exercise itself.

The mechanism behind the improvement of renal function observed after 12 weeks of intervention in the centre-based exercise group cannot be clearly identified. It is possible that the decrease of blood pressure might be involved. Actually, the beneficial effect of aerobic exercise on kidney function has been shown in experimental studies with nephrectomized rats [39] but clinical studies with CKD patients are scarce. Two studies including CKD patients have demonstrated improvement of renal function under a mild-to-moderate-intensity aerobic training [40, 41].

In addition to the body composition and clinical benefits achieved with the aerobic training in the current study, we confirmed significant improvement in the classical physical and functional capacity parameters. This finding is consistent with a number of studies that evaluated the effect of training programmes in dialysis patients [42–46] and in non-dialysed CKD patients [9, 38, 47].

Considering that in-centre closely supervised exercise may not be an option for most patients, in the current study we tested the hypothesis that home-based exercise would provide similar results to those observed in the centre-based exercise group. The benefits achieved for this group of patients on physical capacity were similar to that obtained in the centre-based, and a trend to decrease visceral fat was observed. However, it is important to highlight that home-based exercise was effective in preventing the increase of visceral fat as occurred in the control group. In addition, likewise in the centre-exercise group, the home-based exercise promoted a decrease in blood pressure of the patients confirming the benefits of exercise itself in the control of hypertension. Therefore, although more studies are needed to prove definite effectiveness, we believe that supervised home-based exercise might be a suitable approach for overweight CKD when in centre intervention is not feasible.

A limitation of this study is that the findings are limited to overweight non-dialysed CKD men, so that the results may not be extrapolated for the general CKD population. Nevertheless, the use of an objective end point assessment of visceral fat and the exercise prescription using gold standard methodologies strengthened the significance of the results.

**FIGURE 2:** Percentage of variation in visceral fat and waist circumference after 12 weeks.
In conclusion, we demonstrated that the supervised in-centre exercise programme employed in our study was safe and effective to reduce visceral fat besides promoting relevant clinical benefits in overweight CKD patients.

ACKNOWLEDGEMENTS

We acknowledge the contribution of Dr Antonio Carlos Cordeiro and Dr. Marcelo Costa Batista in the recruitment of patients. This work was supported by Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP no 2009/14786-0), Fundação de Apoio à Universidade Federal de São Paulo (Fap-UNIFESP) and Fundação Oswaldo Ramos.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract form. None declared.

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DNA methylation profile associated with rapid decline in kidney function: findings from the CRIC Study

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**ABSTRACT**

**Background.** Epigenetic mechanisms may be important in the progression of chronic kidney disease (CKD).

**Methods.** We studied the genome-wide DNA methylation pattern associated with rapid loss of kidney function using the Infinium HumanMethylation 450 K BeadChip in 40 Chronic Renal Insufficiency (CRIC) study participants (n = 3939) with...