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Improvement in insulin sensitivity following a 1-year lifestyle intervention program in viscerally obese men: contribution of abdominal adiposity

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ABSTRACT

The objectives of the study were to quantify the effect of a 1-year healthy eating–physical activity/exercise lifestyle modification program on insulin sensitivity in viscerally obese men classified according to their glucose tolerance status and to evaluate the respective contributions of changes in body fat distribution vs changes in cardiorespiratory fitness (CRF) to the improvements in indices of plasma glucose/insulin homeostasis. Abdominally obese, dyslipidemic men (waist circumference ≥90 cm, triglycerides ≥1.69 mmol/L, and/or high-density lipoprotein cholesterol <1.03 mmol/L) were recruited. The 1-year intervention/evaluation was completed by 104 men. Body weight, composition, and fat distribution were assessed by dual-energy x-ray absorptiometry/computed tomography. Cardiorespiratory fitness and cardiometabolic risk profile were measured. After 1 year, insulin sensitivity improved in association with decreases in both visceral (VAT) and subcutaneous adiposity (SAT) as well as with the improvement in CRF, regardless of baseline glucose tolerance. Further analyses were performed according to changes in glucose tolerance status: improvement (group I, n = 39), no change (group N, n = 50), or worsening (group W, n = 15) after 1 year. Groups I and N improved their insulin sensitivity and their CRF, whereas group W did not, while losing less VAT than groups I and N. Multiple regressions showed that reduction in VAT was associated with an improvement in homeostasis model assessment of insulin resistance, whereas reduction in SAT was rather associated with improvement of the insulin sensitivity index of Matsuda. Changes in CRF were not independently associated with changes in indices of plasma glucose/insulin homeostasis. A 1-year lifestyle intervention improved plasma glucose/insulin homeostasis in viscerally obese men, including those with normal glucose tolerance status at baseline. Changes in SAT and VAT but not in CRF appeared to mediate these improvements.

Authors contribution: Anne-Laure Borel: data analysis, data interpretation and manuscript writing. Julie-Anne Nazare: data interpretation and critical revision. Jessica Smith: data interpretation and critical revision. Natalie Alméras: design conception, conduct of the study, and critical revision. Angelo Tremblay: design conception and critical revision. Jean Bergeron: design conception and critical revision. Paul Poirier: design conception and critical revision. Jean-Pierre Després: design conception, conduct of the study, data interpretation, critical revision.

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1. Introduction

Abdominal obesity, characterized by excess visceral adipose tissue (VAT) and ectopic fat deposition, has been associated with a cluster of atherogenic and diabetogenic abnormalities [1]. However, pharmacological approaches to target VAT accumulation are virtually nonexistent since the withdrawal of some of the few available antiobesity drugs [2,3]. Several lifestyle intervention studies using exercise as the treatment modality have shown its ability to mobilize VAT and improve the cardiometabolic risk (CMR) profile, even in the absence of weight loss [4,5]. In the well-known Diabetes Prevention Study (DPS) [6] and Diabetes Prevention Program (DPP) [7], a 58% reduction in the incidence of type 2 diabetes mellitus (T2D) was reported in patients with glucose intolerance following a lifestyle modification program focusing on healthy eating and increased physical activity. However, only few studies have addressed the question of whether it has beneficial effects on indices of plasma glucose/insulin homeostasis specifically among men selected on the basis of their excess visceral adiposity who were further classified on the basis of their glucose tolerance [7-9]. For instance, a recent study has shown that the reduction in T2D's incidence related to physical activity was heterogeneous depending upon the glucose tolerance status of participants assessed at baseline [9].

The present study was designed as a body composition/adipose tissue distribution lifestyle intervention to examine how a healthy eating, physical activity/exercise program could improve the CMR profile of a group of viscerally obese men with the atherogenic dyslipidemia of insulin resistance. Participants did not have T2D; and the study included subjects with both normal and impaired glucose tolerance, aiming at specifically targeting excess visceral adiposity rather than metabolic disturbances. Key inclusion criteria were the presence of abdominal obesity and the high triglyceride/low high-density lipoprotein (HDL) cholesterol atherogenic dyslipidemia that is a lipid phenotype associated with excess VAT [10]. The primary end point of the intervention was visceral adiposity measured by computed tomography. We put forward the hypothesis that a 1-year lifestyle modification program integrating healthy eating habits combined with an increase in physical activity and endurance exercise could lead to improvements in insulin sensitivity, irrespective of patients' glucose tolerance status. We also examined whether changes in body fat distribution vs changes in cardiorespiratory fitness (CRF) would contribute to the improvements in indices of plasma glucose/insulin homeostasis.

2. Methods

2.1. Study design

One hundred forty-four men, between the ages of 30 and 65 years and presenting with abdominal obesity (waist circumference ≥90 cm), triglyceride levels of at least 1.69 mmol/L, and/or HDL cholesterol less than 1.03 mmol/L, were recruited by solicitation in the media to participate to a 3-year lifestyle modification program (the "SYNERGIE" study, to emphasize the synergism between healthy eating and increased physical activity/exercise). Men with T2D, with body mass index (BMI) values less than 25 or greater than 40 kg/m^2, or taking medication targeting glucose or lipid metabolism or blood pressure were excluded. Informed written consent was obtained from all participants before their inclusion in the study that had been approved by the Medical Ethics Committees of Université Laval and of the Institut universitaire de cardiologie et de pneumologie de Québec.

Men were individually counseled once every 2 weeks to improve their nutritional and physical activity/exercise habits during the first 4 months of the program, with subsequent monthly visits. Each visit included an interactive session with a registered nutritionist followed by a meeting with a kinesiologist. The nutritional counseling was adapted to elicit daily energy deficit of about 500 kcal during the first year, which was the "moderate weight loss" phase of SYNERGIE. The daily caloric intake was estimated at baseline and at 1 year by a 3-day dietary record including 1 nonworking day.

The physical activity program was individualized based on men's history and preferences. The goal was to reach 160 min/wk of moderate-intensity endurance exercise that also included, as additional objective, an increase in occupational activity. To help participants to be more active and to monitor themselves between exercise sessions, they were asked to wear a pedometer and to reach a target of 10 000 daily steps.

The present article focuses on the results of the 1-year weight loss phase for the sample of 104 men who completed the first year of intervention, with oral glucose tolerance tests (OGTTs) performed at baseline and 1 year, from the 144 men who initially participated in the study (35 men dropped out during the first year, whereas 5 men did not have OGTT data).

2.2. Anthropometric measurements and body composition

Height, weight, hip circumference [11], and waist circumference [12] were measured according to standardized procedures. Body composition (fat mass and fat-free mass) was assessed by dual-energy x-ray absorptiometry (DEXA) (Lunar Prodigy; GE, Madison, WI). Three sitting blood pressure and pulse rate measurements were taken 3 minutes apart on the nondominant arm with an appropriate cuff size after the patient had been resting in the sitting position for 5 minutes.

2.3. Computed tomography

Cross-sectional areas of VAT and subcutaneous adipose tissue (SAT) were assessed by computed tomography using previously described procedures [13,14]. Calculations of the partial volumes of VAT and SAT between L2-L3 and L4-L5 were performed using the product of the mean of L2-L3 and L4-L5 areas multiplied by the distance separating the 2 slices, as previously described [15].

2.4. Cardiorespiratory fitness

Cardiorespiratory fitness was assessed using a submaximal standardized exercise test on a TMX 425 treadmill (Trackmaster, Newton, KS) linked to a QuarkB2 monitor (Cosmed, Rome, Italy). After a 3-minute warmup at 2.5 mph, 0% slope, the

exercise physiologist adapted the speed and the slope in 3 to 4 steps of 5 minutes each, including a standardized workload of 3.5 mph at 2% slope, to obtain a linear progression to reach between 70% and 80% of the predicted maximal heart rate, which corresponds to approximately 150 beats per minute for all men. According to the American College of Sports Medicine formulas [16], the VO_2 was calculated for each step. In the present study, 2 variables were retained as fitness end points to evaluate CRF: (1) the subject's heart rate (mean of the last 3 minutes) at a standardized treadmill stage (3.5 mph, 2% slope) and (2) the estimated metabolic equivalent of task (MET) reached by the subject at a heart rate of 150 beats per minute.

2.5. *Oral glucose tolerance test*

After a 12-hour overnight fast, participants were subjected to a 75-g oral glucose load. Blood samples were taken at –30, –15, 0, 30, 45, 60, 90, 120, 150, and 180 minutes for the measurement of plasma glucose, insulin, and C-peptide concentrations. Plasma glucose was measured enzymatically [17], whereas plasma insulin [18] and C-peptide [19] were determined by radioimmunoassay. The OGTT was used to define the glucose tolerance status of men: (1) NGT, that is, fasting glucose less than 6.1 mmol/L and 120-minute OGTT glucose less than 7.8 mmol/L; (2) isolated impaired fasting glucose (IFG), that is, fasting glucose greater than or equal to 6.1 and less than 7 mmol/L, and 120-minute OGTT glucose less than 7.8 mmol/L; (3) isolated impaired glucose tolerance (IGT), that is, fasting glucose less than 6.1 mmol/L and 120-minute OGTT glucose greater than or equal to 7.8 and less than 11.1 mmol/L; (4) combined fasting and 120-minute conditions (IFG + IGT); and (5) T2D, that is, fasting glucose greater than or equal to 7 mmol/L or 120-minute OGTT glucose greater than or equal to 11.1 mmol/L [20]. Impaired fasting glucose was defined using 6.1 mmol/L rather than 5.6 mmol/L as a cut point to more specifically define abnormal fasting glucose metabolism leading to T2D [21].

The total glucose, insulin, and C-peptide areas under the curve (AUCs) of OGTT were determined by the trapezoid method between 0 and 120 minutes. Homeostasis model assessment of insulin resistance (HOMA-IR) [22] was calculated from fasting values of glucose and insulin. The insulin sensitivity index of Matsuda (ISI Matsuda) is an OGTT index calculated using formulas adapted from euglycemic-hyperinsulinemic clamp studies [23]. The C-peptide index (0-30) was calculated by the ratio of the increase of C-peptide at 30 minutes to the increase of glucose at 30 minutes. This C-peptide index was used, with AUC C-peptide/AUC glucose ratio, to assess pancreatic insulin secretion independently of hepatic insulin extraction. The insulin secretion to insulin resistance ratio, that is, disposition index, was calculated as the product of insulin secretion measured with AUC C-peptide/AUC glucose and ISI Matsuda. We referred to this disposition index as *DI synergie*. This index was adapted from Abdul-Ghani et al [24].

2.6. *Plasma lipids and lipoproteins and plasma adipokines*

Plasma HDL cholesterol, triglycerides, very low-density lipoprotein (VLDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B were determined according to standardized procedures [25-28]. Plasma leptin and adiponectin concentrations were determined by commercially available enzyme-linked immunosorbent assay kits (B-Bridge, Cupertino, CA).

2.7. *Statistical analyses*

Data are presented as mean ± SD in tables and as mean ± SE in figures. One-way analyses of variance (ANOVAs) with Tukey post hoc analyses were performed to compare groups of men at baseline defined according to baseline glucose tolerance, and then to compare 3 groups of men defined according to the change of glucose tolerance status after 1 year: groups I (improvement), N (no change), and W (worsening). To compare the 1-year changes between groups, a 2-factors ANOVA was performed with one between-subject factor (group) and one within-subject factor (time: baseline vs 1 year), with an interaction term. Pearson correlation coefficients were computed to examine relationships of CMR markers with ISI Matsuda, HOMA-IR, and 120-minute OGTT glucose 1-year changes. The independent and respective contributions of VAT, SAT, and CRF changes to the variance of ISI Matsuda, HOMA-IR, and 120-minute OGTT glucose changes over 1 year were assessed by partial R^2 in multivariable regression models. The hyperbolic relationship between ISI Matsuda (insulin sensitivity index) and AUC C-peptide/AUC glucose (insulin secretion index) was verified on baseline and year 1 values by Pearson correlation after 1/X transformation of ISI Matsuda. The normal distribution of each variable was verified by using Shapiro-Wilk test, and logarithmic transformations were performed in case of skewed distributions. The significance level was set at $P < .05$. All analyses were performed with SAS statistical package version 9.2 (SAS Institute, Cary, NC).

3. Results

From the 144 men who were initially involved in the study, 35 men dropped out during the first year, whereas 5 men did not have complete OGTT data. The men who completed the 1-year intervention/evaluation presented slightly higher BMI (31.2 ± 3.1 vs 30.1 ± 2.8 for the men who completed the 1-year intervention/evaluation vs the men who did not, respectively; $P = .04$), higher fasting insulin (173 ± 74 vs 141 ± 78, respectively; $P = .03$), higher HOMA-IR (6.47 ± 2.95 vs 5.10 ± 2.77, respectively; $P = .01$), and lower ISI Matsuda index (1.40 ± 0.64 vs 2.95 ± 5.91, respectively; $P = .01$) at baseline than the men who did not. The following analyses were therefore conducted on the sample of 104 men who completed the 1-year intervention/evaluation.

3.1. *Response to the lifestyle intervention according to the baseline glucose tolerance status*

Men were classified into subgroups according to their glucose tolerance status at baseline: NGT, IFG, IGT, or IFG + IGT. The characteristics of men in the different subgroups are presented in Table 1. Men with IFG + IGT were older, were more

insulin resistant (with higher HOMA-IR and lower ISI Matsuda), and had more VAT than NGT men. Men with IGT presented a higher BMI, had more SAT and VAT, were more insulin resistant, and had a lower CRF than NGT men. The DI synergie was lower in the IGT and IFG + IGT groups, suggesting an increased risk of T2D in these groups. After 1 year of lifestyle intervention, and as expected, all subgroups had lost body weight and VAT (decreases in VAT volume of −29%, −18%, −23%, and −26% for NGT, IFG, IGT, and IFG + IGT, respectively; $P < .001$) and had improved their CRF (increases in exercise output at 150 beats per minute of +33%, +12%, +22%, and +14% for NGT, IFG, IGT, and IFG + IGT, respectively; $P < .05$). The plasma lipid/lipoprotein profile also improved, as did insulin sensitivity, in all subgroups (increases in the ISI

Table 1 – Characteristics at baseline and 1-year changes of groups defined according to their glucose tolerance status at baseline

	NGT (n = 37)		IFG (n = 15)		IGT (n = 26)		IFG + IGT (n = 26)	
	Baseline	1-y change	Baseline	1-y change	Baseline	1-y change	Baseline	1-y change
Age (y)	45.3 ± 8.2[d]		49 ± 10.6		44.7 ± 8.7[d]		52.5 ± 6.0[ac]	
BMI (kg/m^2)*†	30.5 ± 2.8[c]	−2.2 ± 1.5	30.5 ± 3.4	−1.5 ± 1.9	32.9 ± 2.9[a]	−2.2 ± 1.7	31.1 ± 3.0	−2.3 ± 1.2
Waist girth (cm) *	106.0 ± 8.2	−9.0 ± 5.0	108.9 ± 11.8	−7.1 ± 7.1	111.5 ± 8.8	−7.7 ± 5.7	109.2 ± 7.4	−9.2 ± 4.3
Systolic BP (mm Hg)*†	114 ± 10[d]	−3.3 ± 8.0	118 ± 9	−0.7 ± 11.6	118 ± 10	−3.2 ± 9.7	122 ± 12[a]	−2.6 ± 10.4
Diastolic BP (mm Hg) *	79 ± 7	−5.9 ± 7.5	77 ± 8	−3.3 ± 7.2	78 ± 7	−2.2 ± 7.7	82 ± 6	−5.8 ± 5.9
CT volume of adipose tissue (cm^3)								
Visceral*†	1767 ± 367[cd]	−507 ± 270	1893 ± 529	−339 ± 451	2125 ± 509[a]	−486 ± 389	2121 ± 450[a]	−555 ± 337
Subcutaneous *	1643 ± 528	−336 ± 261	1888 ± 840	−298 ± 286	2061 ± 727	−360 ± 299	1685 ± 494	−281 ± 223
DEXA								
Fat-free mass (kg) *	65.7 ± 7.1	−0.9 ± 1.3	63.3 ± 8.0	−0.3 ± 1.7	65.3 ± 6.8	−0.6 ± 2.1	67.3 ± 6.8	−1.1 ± 1.9
Fat mass (kg)*†	27.0 ± 6.4[c]	−5.9 ± 3.8	30.1 ± 7.8	−4.2 ± 5.0	33.2 ± 6.9[a]	−6.2 ± 3.5	29.4 ± 6.7	−6.2 ± 3.2
Plasma lipids/lipoproteins								
Triglycerides (mmol/L) *	2.39 ± 0.99	−0.68 ± 0.89	2.26 ± 0.52	−0.24 ± 0.77	2.71 ± 0.78	−0.48 ± 0.77	2.56 ± 1.12	−0.66 ± 0.99
VLDL chol (mmol/L) *	0.99 ± 0.45	−0.34 ± 0.38	0.90 ± 0.24	−0.18 ± 0.31	1.19 ± 0.40	−0.26 ± 0.37	1.09 ± 0.65	−0.35 ± 0.47
LDL chol (mmol/L)	3.14 ± 0.69	+0.16 ± 0.41	2.99 ± 0.59	−0.00 ± 0.62	3.05 ± 0.62	+0.19 ± 0.62	3.28 ± 0.78	+0.06 ± 0.72
HDL chol (mmol/L) *	0.98 ± 0.19	+0.13 ± 0.15	0.86 ± 0.11	+0.12 ± 0.12	0.94 ± 0.16	+0.10 ± 0.10	0.99 ± 0.19	+0.13 ± 0.14
Apolipoprotein B (g/L)	1.07 ± 0.17	−0.05 ± 0.13	1.06 ± 0.13	−0.06 ± 0.18	1.10 ± 0.19	+0.01 ± 0.16	1.14 ± 0.20	−0.07 ± 0.15
Chol total/HDL chol *	5.30 ± 0.95	−0.66 ± 0.75‡	5.57 ± 0.86	−0.73 ± 1.05†	5.60 ± 0.86	−0.47 ± 0.73 *	5.54 ± 1.10	−0.80 ± 0.85
Plasma glucose/insulin homeostasis								
AUC glucose *†‡ (mmol/L × 120 min)	964± 105[cd]	−81 ± 148 *	1034 ±128[cd]	+59 ± 220	1130 ±130[abd]	−94 ± 123†	1236 ± 145[abc]	−142 ± 138‡
AUC insulin *† (nmol/L × 120 min)	120 ± 46	−47 ± 45	134 ± 56	−44 ± 46	138 ± 53	−56 ± 48	152 ± 53	−56 ± 40
AUC C-peptide *† (nmol/L × 120 min)	573 ± 155	−86 ± 140†	616 ± 135	−61 ± 158	646 ± 197	−122 ± 164†	678 ± 161	−97 ± 142†
HOMA-IR *†‡	5.2 ± 2.4[d]	−1.6 ± 2.4‡	6.5 ± 2.5	−1.6 ± 2.6 *	6.0 ± 2.2[d]	−1.8 ± 2.2†	8.7 ± 3.4[ac]	−4.2 ± 3.2‡
ISI Matsuda *†	1.7 ± 0.7[d]	+1.0 ± 1.0	1.4 ± 0.6	+0.7 ± 1.0	1.3 ± 0.5	+0.8 ± 0.7	1.1 ± 0.6[a]	+0.8 ± 0.5
C-peptide index$_{(0\text{-}30\ min)}$†	966 ± 384	209 ± 947	917 ± 428	−220 ± 386	903 ± 425	−45 ± 412	712 ± 271	−14 ± 322
AUC$_{C\text{-}peptide}$/AUC$_{glucose}$ *	598 ± 159	−41 ± 149	599 ± 142	−94 ± 106 *	576 ± 180	−62 ± 127 *	546 ± 131	−20 ± 143
DI synergie *†‡	954 ± 310[cd]	+495 ± 692‡	792 ± 341	+164 ± 492	709 ± 210[a]	+330 ± 357‡	554 ± 270[a]	+425 ± 337‡
Adipokines								
Adiponectin (μg/mL) *	3.7 ± 1.5	+0.6 ± 1.1	4.1 ± 2.0	+1.2 ± 1.4	3.6 ± 1.0	+0.6 ± 0.8	3.7 ± 1.3	+0.7 ± 0.9
Leptin (ng/mL) *	9.5 ± 4.6	−3.0 ± 3.4	14.7 ± 14.4	−1.8 ± 4.9	14.1 ± 8.1	−4.3 ± 4.0	13.3 ± 7.0	−5.1 ± 4.5
Submaximal treadmill exercise								
Heart rate, 3.5 mph; 2% *† (beats/min)	115 ± 14[c]	−15 ± 11	118 ± 14[c]	−7 ± 15	127 ± 12[abd]	−16 ± 11	114 ± 11[c]	−12 ± 8
Exercise output at 150 beats/min (METs) *†	7.7 ± 1.4	+1.7 ± 1.1	7.4 ± 1.5	+0.8 ± 1.8	6.8 ± 1.4[d]	+1.3 ± 1.4	7.9 ± 1.4[c]	+1.2 ± 1.3
Physical activity level and daily caloric intake								
Daily step count * (number of steps/d)	8151 ± 3124	+1494 ± 2186	8819 ± 2766[c]	+620 ± 2998	6480 ± 2763[b]	+2537 ± 2691	6938 ± 1808	+2611 ± 3038
Daily caloric intake * (kcal/d)	2997 ± 589	−471 ± 636	3268 ± 932	−711 ± 744	3073 ± 426	−677 ± 456	2989 ± 737	−487 ± 793

Data are presented as mean ± SD. BMI indicates body mass index, BP, blood pressure, chol, cholesterol, ISI, insulin sensitivity index, DI, disposition index, AUC, area under the curve, CT, computed tomography. Differences between groups at baseline were assessed by 1-way ANOVA and Tukey post hoc analyses. Superscript letters refer to statistically significant differences ($P < .05$) between subgroups: a = NGT, b = IFG, c = IGT, d = IFG + IGT. Data are then compared by ANOVA repeated measure.

* Reports P value for a time effect < .05.

† Reports P value for a group effect < .05.

‡ Reports P value for a significant time × group interaction < .05 in the left column. In case of significant time × group interaction, group-specific 1-year changes are reported in each "1-y change" column, with *$P < .05$, †$P < .001$, and ‡$P < .0001$.

Matsuda of +58%, +51%, +58%, and +80% for NGT, IFG, IGT, and IFG + IGT, respectively; $P < .05$).

3.2. *Evolution of glucose tolerance status after the 1-year intervention*

Fig. 1 summarizes the changes in glucose tolerance status observed in all subgroups after the 1-year lifestyle intervention. From these results, we redefined 3 subgroups according to the subjects' changes in glucose tolerance status: group I (improvement), group N (no change), and group W (worsening) (Fig. 1).

Men of group I, N, or W were not different regarding assiduity to the nutritional or physical activity appointments. Baseline as well as 1-year changes in daily caloric intakes and daily step counts were not different between the 3 groups (Table 2).

The baseline characteristics and 1-year changes of groups I, N, and W are presented in Table 2. At baseline, groups were not different regarding age, BMI, VAT, plasma lipid/lipoprotein profile, or CRF. Men of group W had a lower total fat mass and less SAT than group I. Group I presented a higher insulin resistance (HOMA-IR and ISI Matsuda) and a higher AUC glucose and AUC C-peptide than groups N and W, whereas their DI synergie was lower, suggesting a higher risk to develop T2D. After 1 year of lifestyle intervention, group W had a smaller decrease in BMI, waist circumference, VAT, SAT, and total fat mass than groups I and N (Table 2, Fig. 2A). As opposed to both groups I and N, no improvement in CRF was noted in group W (Fig. 2B). Accordingly, triglyceride levels and diastolic blood pressure did not change in group W, whereas they decreased in both groups I and N. The HOMA-IR and ISI Matsuda indices were improved in groups I and N, whereas they did not change in group W. DI synergie increased in groups I and N but not in group W, suggesting that the risk of T2D was reduced in groups I and N with no significant change in group W.

In Fig. 2C, both components of the DI synergie, ISI Matsuda and AUC C-peptide/AUC glucose, are plotted for each group as X and Y values, respectively. The relationship of ISI Matsuda to AUC C-peptide/AUC glucose was found to be hyperbolic; and 2 hyperbolic regression lines, calculated from data of NGT men and IFG + IGT men at baseline, are presented on the graph. The evolution of group I over the 1-year lifestyle intervention crossed the regression line of NGT subgroup values at baseline. Therefore, at the end of the year, the insulin sensitivity of group I reached that of the NGT group at baseline, with an appropriate change in insulin secretion. At baseline, group N was superimposed to the NGT men's regression line, but nevertheless improved after the 1-year intervention, as did group I. On the contrary, neither insulin sensitivity of group W nor insulin secretion changed significantly over the intervention period. Moreover, the 1-year insulin sensitivity and insulin secretion indices of group W tended to reach the baseline values of the IFG + IGT men.

3.3. *Regression analyses*

When the whole sample of 104 men was analyzed, changes in ISI Matsuda over the 1-year lifestyle intervention were negatively correlated with changes in SAT, VAT, and total fat mass ($r = -0.48$, $r = -0.44$, and $r = -0.58$, respectively; $P < .0001$) and positively correlated with the improvement in CRF ($r = 0.37$

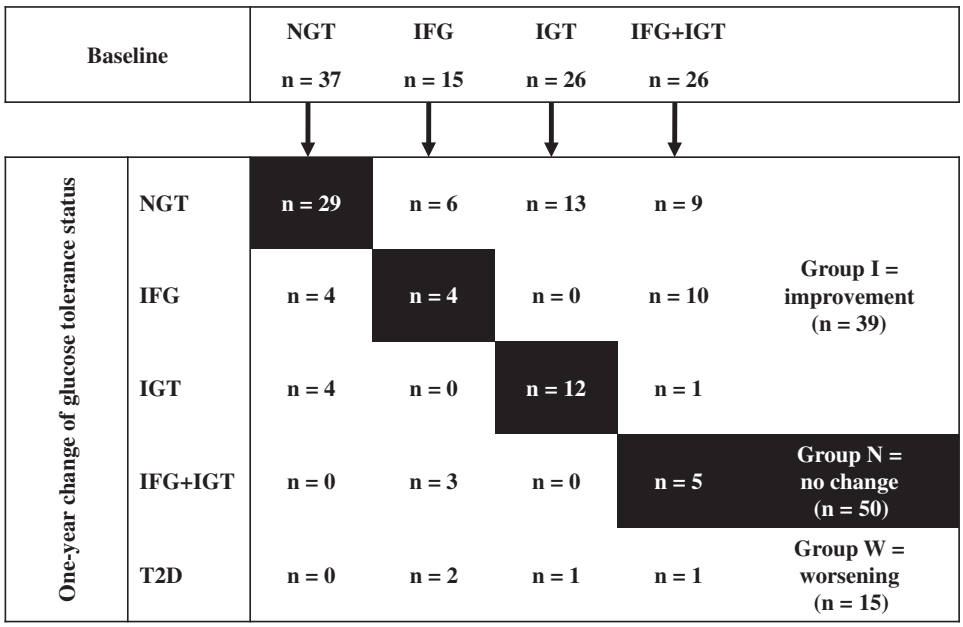

Fig. 1 – Glucose tolerance status of men at baseline and evolution after 1 year of lifestyle intervention. Each man was classified according to the evolution of his glucose tolerance status after 1 year of lifestyle intervention (group I: improvement, group N: no change, group W: worsening, respectively). *Improvement* was defined as IFG change to NGT; IGT change to NGT; or IFG + IGT change to IFG, IGT, or NGT. *No change* was defined as men who stayed in the same glucose tolerance status. *Worsening* was defined as NGT change to IFG, IGT, IFG + IGT, or T2D; IFG change to IFG + IGT or T2D; IGT change to IFG + IGT or T2D; and IGT + IFG change to T2D.

Table 2 – Characteristics at baseline and 1-year changes of groups defined according glucose tolerance status evolution after 1 year

	Group I (improvement n = 39)		Group N (no change n = 50)		Group W (worsening) (n = 15)	
	Baseline	1-y change	Baseline	1-y change	Baseline	1-y change
Age (y)	48.8 ± 8.7		45.9 ± 8.7		49.6 ± 8.3	
BMI (kg/m^2) * ‡	31.5 ± 3.0	−2.4 ± 1.4‡	31.3 ± 3.3	−2.4 ± 1.6‡	30.1 ± 2.3	−0.8 ± 1.1*
Waist girth (cm) * ‡	109.8 ± 9.0	−8.7 ± 4.5‡	108.9 ± 9.1	−9.3 ± 6.0‡	104.7 ± 7.1	−4.6 ± 3.7*
Systolic BP (mm Hg)	120 ± 11	−4.3 ± 9.1	116 ± 10	−2.6 ± 9.7	116 ± 11	+1.4 ± 9.6
Diastolic BP (mm Hg) * ‡	81 ± 7	−6.1 ± 5.3‡	78 ± 7	−4.7 ± 7.8‡	77 ± 7	+0.0 ± 8.4
CT: volume of adipose tissue (cm^3)						
Visceral * ‡	2051 ± 517	−561 ± 328‡	1942 ± 437	−517 ± 334‡	1819 ± 469	−191 ± 338
Subcutaneous * ‡	1866 ± 663[c]	−350 ± 243‡	1862± 672[c]	−355 ± 280‡	1402 ± 302[ab]	−145 ± 201*
DEXA						
Fat-free mass (kg) *	66.3 ± 6.8	−1.1 ± 2.0†	66.0 ± 7.6	−0.8 ± 1.7*	63.0 ± 6.1	+0.1 ± 1.0
Fat mass (kg) * ‡	30.9 ± 6.6[c]	−6.3 ± 3.5‡	29.8 ± 7.6	−6.5 ± 3.7‡	25.7 ± 5.6[a]	−2.5 ± 3.1*
Plasma lipids/lipoproteins						
Triglycerides (mmol/L) * ‡	2.59 ± 1.01	−0.69 ± 0.92‡	2.49 ± 0.94	−0.63 ± 0.82‡	2.24 ± 0.55	+0.04 ± 0.70
VLDL chol (mmol/L) * ‡	1.12 ± 0.56	−0.35 ± 0.45‡	1.04 ± 0.43	−0.32 ± 0.35‡	0.92 ± 0.38	−0.08 ± 0.30
LDL chol (mmol/L) *	3.10 ± 0.70	+0.08 ± 0.71	3.18 ± 0.69	+0.11 ± 0.48	3.08 ± 0.65	+0.25 ± 0.53
HDL chol (mmol/L) *	0.95 ± 0.17	+0.12 ± 0.14	0.97 ± 0.18	+0.13 ± 0.14	0.93 ± 0.15	+0.09 ± 0.10
Apolipoprotein B (g/L) *	1.09 ± 0.20	−0.05 ± 0.17	1.10 ± 0.17	−0.05 ± 0.14	1.07 ± 0.16	+0.03 ± 0.15
Chol total/HDL chol *	5.53 ± 0.98	−0.75 ± 0.89‡	5.47 ± 0.98	−0.71 ± 0.75‡	5.34 ± 0.79	−0.24 ± 0.77
Plasma glucose/insulin homeostasis						
AUC glucose (mmol/L × 120 min) * † ‡	1156 ± 165[bc]	−128 ± 138‡	1048 ± 156[a]	−104 ± 135‡	1022 ± 134[a]	+111 ± 166*
AUC insulin (nmol/L x 120 min) * ‡	147 ± 53	−60 ± 40‡	129 ± 48	−50 ± 41‡	122 ± 55	−32 ± 60*
AUC C-peptide (nmol/L x 120 min) * ‡	673 ± 167[c]	−132 ± 140‡	611 ± 166	−102 ± 133‡	538 ± 148[a]	+20 ± 160
HOMA-IR * ‡	7.6 ± 3.1[bc]	−3.5 ± 2.8‡	5.9 ± 2.8[a]	−2.0 ± 2.7‡	5.5 ± 2.1[a]	−0.2 ± 1.5
ISI Matsuda * ‡	1.2 ± 0.5[b]	+1.0 ± 0.7‡c	1.5 ± 0.7[a]	+1.0 ± 0.9‡	1.6 ± 0.7	+0.1 ± 0.6
C-peptide index$_{(0\text{-}30\ min)}$	825 ± 406	−68 ± 410	946 ± 365	+151 ± 834	812 ± 385	−108 ± 408
AUC C-peptide/AUC glucose *	586 ± 153	−58 ± 141	591 ± 161	−43 ± 134	528 ± 139	−38 ± 145
DI synergie * † ‡	661 ± 287[b]	+448 ± 364‡	842 ± 324[a]	+481 ± 614‡	810 ± 327	−5 ± 362
Adipokines						
Adiponectin (μg/mL) *	3.8 ± 1.6	+0.9 ± 1.2	3.8 ± 1.4	+0.6 ± 1.0	3.4 ± 1.3	+0.6 ± 0.9
Leptin (ng/mL) * ‡	12.8 ± 6.2	−4.5 ± 3.9‡	12.3 ± 8.7	−4.1 ± 4.0‡	11.6 ± 11.4	−0.3 ± 4.0
Submaximal treadmill exercise						
Heart rate, 3.5 mph; 2% (beats/min) * ‡	118 ± 12	−14 ± 11‡	120 ± 14	−16 ± 11‡	112 ± 14	−2 ± 7
Exercise output at 150 beats/min (METs) * ‡	7.5 ± 1.3	+1.2 ± 1.3‡	7.3 ± 1.6	+1.8 ± 1.3‡	8.0 ± 1.2	+0.2 ± 1.1
Physical activity level and daily caloric intake						
Daily step count (number of steps/d) *	7351 ± 2475	+1828 ± 2725	7825 ± 2998	+2093 ± 2958	6836 ± 2987	+2339 ± 2272
Daily caloric intake (kcal/d) *	2549 ± 567	−535 ± 672	3070 ± 612	−596 ± 542	2875 ± 697	−531 ± 985

Data are mean ± SD. BMI indicates body mass index, BP, blood pressure, chol, cholesterol, ISI, insulin sensitivity index, DI, disposition index, AUC, area under the curve, CT, computed tomography. Differences between groups at baseline were assessed by 1-way ANOVA and Tukey post hoc analyses. Superscript letters refer to statistically significant differences ($P < .05$) between subgroups: a = NGT, b = IFG, c = IGT, d = IFG + IGT. Data are then compared by ANOVA repeated measure.

* Reports P value for a time effect < .05.

† Reports P value for a group effect < .05.

‡ Reports P value for a significant time × group interaction < .05 in the left column. In case of significant time × group interaction, group-specific 1-year changes are reported in each "1-y change" column, with *$P < .05$, †$P < .001$, and ‡$P < .0001$.

for exercise output at 150 beats per minute, $P = .0003$) (Table 3). Changes in ISI Matsuda were also positively correlated with changes in HDL cholesterol ($r = 0.31$, $P = .002$) and in adiponectin ($r = 0.25$, $P = .01$) levels and negatively correlated with changes in triglyceride ($r = –0.41$, $P < .0001$), apolipoprotein B ($r = –0.22$, $P = .03$), and leptin ($r = –0.32$, $P = .001$) levels. These associations followed the same trends when 2 other indices of plasma glucose/insulin homeostasis, HOMA-IR and the 120-minute OGTT-glucose, were analyzed instead of ISI Matsuda.

A multivariable regression model was used to evaluate the relative contributions of changes in VAT, SAT, and CRF to changes in ISI Matsuda. Change in SAT was the only independent factor associated with change in ISI Matsuda over the 1-year intervention ($R^2 = 0.24$, $P < .0001$). Using the same model, only changes in VAT independently contributed to the variance of 1-year changes in HOMA-IR ($R^2 = 0.15$, $P = .0002$) and in the 120-minute OGTT glucose level ($R^2 = 0.18$, $P < .0001$).

4. Discussion

The present study is not a randomized trial to quantify the effects of a lifestyle modification program on the CMR profile. Indeed, whether a lifestyle modification program can improve the CMR profile has already been very well documented [6-7,29-32]. Instead, the present study was designed to test

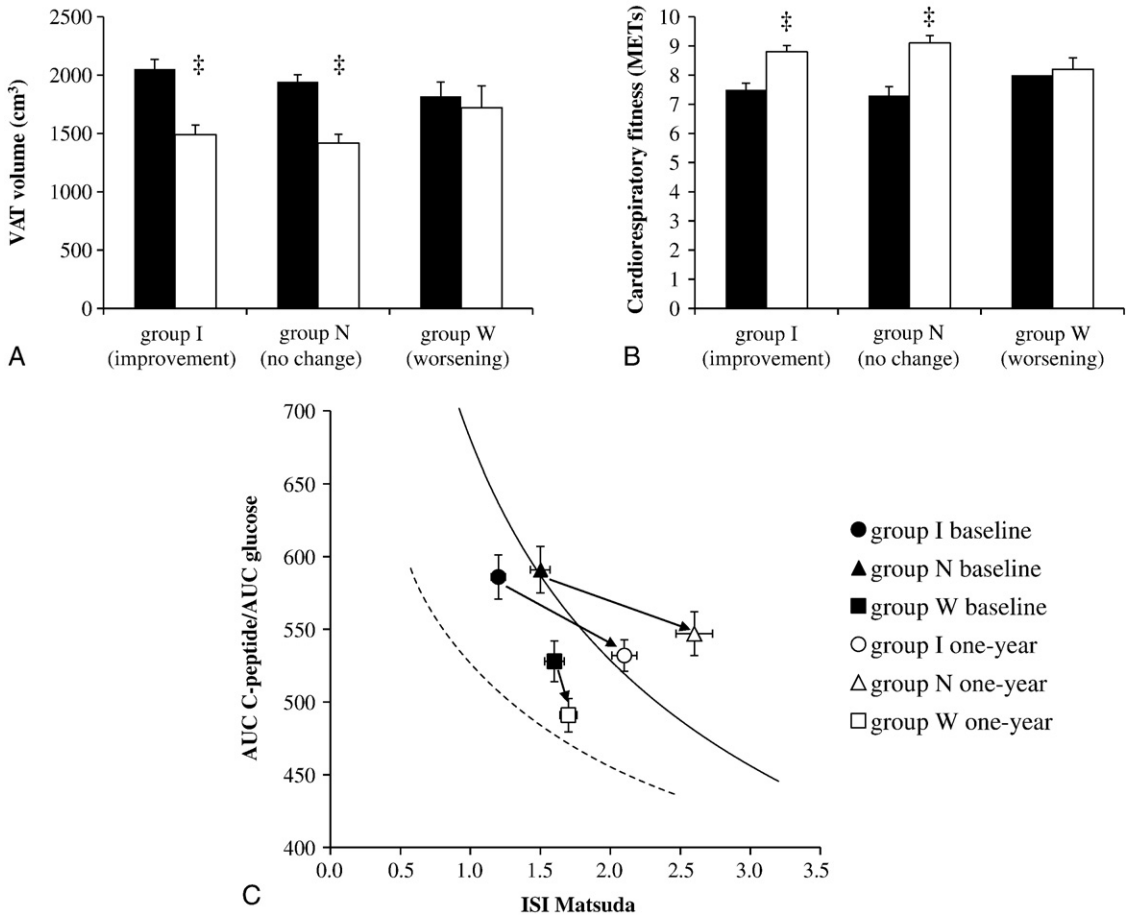

Fig. 2 – Effects of lifestyle intervention in subgroups defined according to the glucose tolerance status evolution after 1 year. A, Subgroup changes in visceral adipose tissue (VAT) volume (cubic centimeter) between baseline (black column) and year 1 (white column). B, Subgroup changes in CRF as defined by the exercise output when heart rate reached 150 beats per minute during submaximal test (metabolic equivalent of task): baseline (black column) and year 1 (white column). C, Subgroup changes in insulin sensitivity (ISI Matsuda) and insulin secretion (AUC C-peptide/AUC glucose). The curves represent the hyperbolic regression lines between baseline ISI Matsuda and AUC C-peptide/AUC glucose in NGT (continued line) and IGT + IFG (discontinued line) men. The lower the insulin secretion for any given insulin sensitivity, the greater is the risk of T2D, as illustrated by the regression line of IFG + IGT men that is markedly lower than the regression line of NGT men. ‡$P < .0001$.

whether a 1-year healthy eating–physical activity/exercise program would change the insulin sensitivity of viscerally obese dyslipidemic men, regardless of their glucose tolerance status at baseline. We also explored which factor(s) could be related to the lack of improvement in glucose tolerance after this 1-year intervention and whether improvements in indices of plasma glucose/insulin homeostasis and in CMR variables were related to losses of either VAT or SAT, or to the improvement in CRF. An original aspect of this study was the detailed imaging measurement of body composition by DEXA and of fat distribution (abdominal visceral vs subcutaneous adiposity) by computed tomography, combined with direct measurement of CRF and exercise training volume in a specific sample of sedentary, viscerally obese, dyslipidemic men.

Indeed, compared with the DPS [6] and DPP [7] studies, the present study did not select men on the basis of glucose tolerance status but instead specifically recruited viscerally obese dyslipidemic men based on the rationale that VAT accumulation, irrespective of glucose tolerance, is a key phenotype leading to a cluster of cardiovascular and metabolic complications [1]. Among these viscerally obese dyslipidemic men, the glucose tolerance status was heterogeneous at baseline, with approximately one third of them having NGT, whereas others presented with a variety of abnormal glucose tolerance status. After 1 year of healthy eating and exercise/physical activity lifestyle intervention, both VAT and SAT decreased and CRF improved, as expected. These improvements were all associated with an increase in insulin sensitivity, as well as with an improvement in CMR profile, in subjects with NGT as well as in subjects with IFG and/or IGT.

4.1. *Evolution of plasma glucose/insulin homeostasis according to baseline and 1-year glucose tolerance status*

Similar to what has been demonstrated in previous studies [33,34], a hyperbolic function between insulin sensitivity and

Table 3 – Univariate regressions between 1-year changes in CMR markers and changes in HOMA-IR, ISI Matsuda indices, and 120-minute OGTT glucose

1-y change	1-y change		
	Log HOMA-IR	Log ISI Matsuda	120-min OGTT glucose
Age	NS	−0.20*	0.22*
BMI	0.45‡	−0.52‡	0.38‡
Waist girth	0.44‡	−0.48‡	0.38‡
Systolic BP	NS	NS	0.21*
Diastolic BP	0.23*	−0.28*	0.24*
CT: L4-L5 cross-sectional areas of adipose tissue			
Visceral	0.38‡	−0.34†	0.36†
Subcutaneous	0.35†	−0.53‡	0.33†
CT: volume of adipose tissue			
Visceral	0.41‡	−0.44‡	0.39‡
Subcutaneous	0.30*	−0.48‡	0.29*
DEXA			
Free-fat mass	NS	0.24*	0.20*
Fat mass	0.45‡	−0.58‡	0.42‡
Plasma lipids/lipoproteins			
Log triglycerides	0.29*	−0.41‡	0.34†
Log VLDL chol	0.27*	−0.33†	0.24*
LDL	NS	NS	NS
HDL chol	−0.23*	0.31*	NS
Apolipoprotein B	NS	−0.22*	NS
Chol total/HDL chol	0.31*	−0.37†	NS
Adipokines			
Adiponectin	−0.35†	0.25*	NS
Leptin	−0.39†	−0.32‡	0.31*
Submaximal treadmill exercise			
Heart rate, 3.5 mph; 2% slope	0.27*	−0.40‡	0.41‡
Exercise output at 150 beats/min	NS	0.37†	−0.31*
Physical activity level and daily caloric intake			
Daily step count	NS	NS	NS
Daily caloric intake	NS	NS	NS

Pearson univariate correlations were performed to compute relationships of CMR markers with ISI Matsuda, HOMA-IR, and 120-minute OGTT glucose 1-year changes. Significant correlations are reported by *$P < .05$, †$P < .001$, and ‡$P < .0001$.

insulin secretion was found at baseline in these viscerally obese men. With improved insulin sensitivity, there is obviously a need for less insulin secretion to manage the same glucose disposal. When glucose tolerance deteriorates, the hyperbolic curve shifts to the left and downward; and this was observed in subjects with combined IFG + IGT compared with subjects with NGT. Men who either improved or maintained their glucose tolerance status after 1 year substantially improved, in both cases, their global insulin sensitivity (ISI Matsuda); and as a consequence, their insulin secretion decreased. Men whose glucose tolerance deteriorated after 1 year had change in neither insulin sensitivity nor insulin secretion. When plotted on the graph representing the hyperbolic function between insulin sensitivity and insulin secretion, subjects showing an improvement or no change of glucose tolerance status after 1 year shifted to the right and upward the regression line observed among NGT subjects at baseline. However, subjects who worsened their glucose tolerance status did not show such beneficial adaptation. Thus, the product of ISI Matsuda and AUC C-peptide/AUC glucose was computed as a composite measure of the plasma glucose/insulin homeostasis. This disposition index (DI synergie) decreased progressively from NGT to IFG + IGT at baseline and increased in subjects who improved or maintained their glucose tolerance status after 1 year. Such a composite disposition index has been used in a previous study of Utzschneider et al [33] with the product of different indices of insulin sensitivity (1/fasting insulin) and insulin secretion (Δinsulin 30-0 minute/Δglucose 30-0 minute). In this previous study, it was shown that a higher disposition index was associated with a decreased risk of developing T2D at 10 years. Therefore, an increase in the DI synergie in our viscerally obese men could suggest a lower risk of developing T2D after 1 year of intervention.

4.2. *Low responders for the improvement in glucose tolerance*

Among those who completed the 1-year intervention, worsening of glucose tolerance was only observed in 15 of the 104 men. The comparison of these 15 men who deteriorated their plasma glucose homeostasis with those who did not change (n = 50) or improved (n = 39) their glucose tolerance status should be interpreted with caution because the difference in number of subjects by groups led to an unbalanced ANOVA analysis. Despite this caveat, substantial differences were noted between groups, suggesting that deterioration of glucose tolerance among the nonresponders was the result

of unchanged insulin sensitivity after 1 year. These men failed to improve their CRF and they lost less body fat compared with the other subgroups of men despite equal adherence to the physical training sessions, comparable increases in daily step count, similar number of diet appointments, and equal decreases in estimated daily caloric intake. Thus, these men could be considered as "low responders" without presumed reason as to why they failed. Therefore, it appears that an improvement in CRF may be necessary to improve insulin sensitivity and, consequently, to decrease T2D risk, whereas a 12% decrease in VAT and a 10% decrease in SAT were not associated with improvements of indices of plasma glucose/insulin homeostasis in these "nonresponders." In a substudy of DPS that focused on acute measurement of insulin sensitivity by intravenous load tests [35], subjects who lost weight after 4 years had a substantial improvement in insulin sensitivity, whereas subjects who gained weight during the same period had a decrease in insulin sensitivity. Similar conclusions were reached for other CMR markers, implying that a sufficient body weight/VAT loss is necessary to achieve a significant improvement in CMR profile in response to a lifestyle intervention [36]. In the present study, men who did not improve their insulin sensitivity did not appear to be less compliant to the program. One possible explanation could be that these low responders had an unfavorable "gene-lifestyle" interaction profile because several studies have demonstrated that genetic variation could affect the response to lifestyle intervention in terms of weight loss and lowering the risk of T2D [37,38].

4.3. *Contribution of the change in CRF to the improvement in insulin sensitivity*

The ability of physical activity alone to improve insulin sensitivity has been shown to be variable in the published literature [39,40]. However, in combination with diet interventions, physical activity either enhances the ability of diet to improve insulin sensitivity [41] or allows long-term maintenance of weight loss [42]. In the present study, the improvement in insulin sensitivity over the 1-year intervention was positively correlated with the improvement in CRF. However, in multivariable regression models including VAT, SAT, and CRF changes, CRF did not appear to be independently associated with insulin sensitivity changes, suggesting that the effect of fitness on insulin sensitivity was largely mediated by the loss of body fat/VAT.

4.4. *Specific contributions of changes in VAT and SAT to the improvement in insulin sensitivity*

Several studies have compared the specific effects of VAT vs SAT losses on insulin sensitivity, with divergent results [43-45]. In the present study, VAT reduction was independently associated with 1-year reduction in HOMA-IR and in 120-minute OGTT glucose, whereas changes in the ISI Matsuda index were independently associated with changes in SAT. These insulin sensitivity indices reflect different aspects of insulin resistance, and this could explain their different associations with changes in VAT and SAT. The HOMA-IR is calculated from the fasting glucose and insulin levels and may be more closely related to excessive hepatic glucose production than ISI Matsuda, which has been developed from the ISI index of clamp studies and therefore may be more reflective of muscle insulin resistance [46]. Thus, the specific role of VAT or SAT in developing insulin resistance could depend on the target organ considered, that is, hepatic or muscle insulin resistance, respectively.

4.5. *Strengths and weaknesses of the study*

The first limitation of this study is its being uncontrolled. Therefore, the relationships found between VAT and SAT decreases, or CRF increase and the improvement in glucose/insulin homeostasis are associative. A randomized controlled trial would be necessary to provide further evidence for a causal relationship. One strength of the study is to have conducted an integrated and synergistic lifestyle intervention program, combining a long-term moderate caloric restriction with an increased in moderate-intensity endurance exercise and in occupational activity. This lifestyle modification program was also designed so that its cost would make it affordable in routine clinical practice. However, one limit of this design is that physical activity did not involve strength training that is likely to increase muscle mass, contributing to enhance energy expenditure, muscle, and global insulin sensitivity [47], which is now recommended in guidelines on physical activity [48]. Further studies should be designed to compare the efficacy of strength training vs endurance training regarding changes in body composition/fat distribution and the related improvements in plasma glucose/insulin homeostasis in viscerally obese dyslipidemic individuals. Moreover, such a study should be randomized with a crossover design to test the hypothesis that individuals who are low responders to one exercise modality could be responsive to the other approach. Another limitation of this study is the evaluation of daily caloric intake by a 3-day dietary record, which is notoriously known to underestimate the caloric intake [49]. However, this evaluation was made at baseline and repeated at 1 year. Thus, the expected underestimation most likely did not interfere with the evaluation of the 1-year change in daily caloric intake.

5. Conclusion

The present 1-year healthy eating–physical activity/exercise intervention program substantially improved indices of plasma glucose/insulin homeostasis in viscerally obese dyslipidemic men, regardless of their glucose tolerance status at baseline. As a consequence, the majority of participants improved or stabilized their glucose tolerance status over the 1-year intervention. However, lack of CRF improvement and limited losses in VAT and SAT defined a subgroup of subjects who failed to improve their insulin sensitivity and who worsened their glucose tolerance status after 1 year. Reduction in VAT appeared to be predominantly associated with the improvement of indices possibly reflecting more hepatic insulin sensitivity, whereas reduction in SAT was associated with improvements in indices reflecting muscle/global insulin sensitivity. Our

findings are concordant with the notion that healthy eating and increased physical activity/exercise are relevant approaches to improve insulin sensitivity and presumably lower the risk of T2D in viscerally obese men. It appears that such beneficial effects are largely mediated by the reduction in VAT and SAT and not by the improvement in CRF.

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Conflict of Interest

No conflict of interest.

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