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Clinical Research

Intensive Lifestyle Intervention Improves Cardiometabolic and Exercise Parameters in Metabolically Healthy Obese and Metabolically Unhealthy Obese Individuals

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ABSTRACT

Background: The effects of an intensive lifestyle intervention including Mediterranean diet nutritional counselling and high-intensity interval training (HIIT) on body composition, cardiometabolic, and exercise parameters were studied in metabolically unhealthy obese (NMHO) and metabolically healthy but obese (MHO) subjects.

Methods: Fifty-five MHO (51 ± 8 years; waist circumference, 109 ± 13 cm) and 79 NMHO subjects (54 ± 9 years; waist circumference, 112 ± 13 cm) participated in an intensive lifestyle modification program based on Mediterranean diet nutritional counselling and HIIT 2-3 times per week. Body composition, cardiometabolic, and exercise parameters were measured at baseline and after 9 months.

Results: Initially, MHO patients had a lower blood pressure (BP), fasting glycemia, triglycerides, and a higher high-density lipoprotein

RÉSUMÉ

Introduction : Les effets d'une intervention intensive sur le mode de vie incluant des conseils nutritionnels sur la diète méditerranéenne et de l'entraînement par intervalles à haute intensité (EIHI) sur la composition corporelle, les paramètres cardiométaboliques et d'effort, ont été étudiés chez des sujets obèses avec syndrome métabolique (OSM) et des sujets obèses sans syndrome métabolique (OSSM).

Méthodes : Cinquante-cinq (55) sujets OSSM (51 ± 8 ans; tour de taille, 109 ± 13 cm) et 79 sujets OSM (54 ± 9 ans; tour de taille, 112 ± 13 cm) ont participé à un programme intensif de modification du mode de vie incluant des conseils nutritionnels sur la diète méditerranéenne et de et l'EIHI de 2 à 3 fois par semaine. La composition corporelle, et les paramètres cardiométaboliques et d'effort ont été mesurés au début et après 9 mois.

The prevalence of obesity is dramatically increasing, reaching approximately 25% in Canada[1] and 35% in the United States.[2] Obesity is associated with important comorbidities, like cardiovascular (CV) disease (CVD), type 2 diabetes, stroke, hypertension, osteoarthritis, and cancer.[1] Some obese patients have been characterized as "metabolically healthy but obese (MHO)," based on a more favourable metabolic profile and a higher fitness level vs metabolically unhealthy obese (NMHO) counterparts.[3,4] Previous studies on lifestyle intervention in MHO and NMHO patients have led to conflicting results. Two studies in women using 3- and 6-month calorie-restricted diets showed a modest reduction in fat mass in MHO and NMHO groups,[5,6] but either no effect on insulin sensitivity and lipid parameters[6] or decreased insulin sensitivity in MHO women.[5] Conflicting results were reported for exercise training in 2 studies of MHO and NMHO women.[7,8] Janiszewski and Ross[9] demonstrated improvement in multiple parameters after 3 to 6 months of moderate intensity continuous aerobic exercise training (MICET) or energy-restricted diet. Only 1 study[10] assessed a longer-term lifestyle intervention (9 months) combining a calorie-restricted diet with MICET, showing reduced visceral fat and body mass (waist circumference [WC]) in both groups, reduced insulin resistance only in the NMHO group, and no effect on lipid parameters in either group.

The Mediterranean diet reduces major cardiovascular events in high CV risk individuals[11] and causes long-term reductions of body mass in obese patients.[12] Furthermore, a 12-week calorie-restricted Mediterranean-like diet similarly improved body composition, insulin resistance, hepatic enzymes, and leptin levels.[13] Another short-term study showed that combining a Mediterranean diet with moderate- to high-intensity aerobic training was more effective than the Mediterranean diet alone in improving metabolic syndrome

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cholesterol and peak oxygen uptake (VO_2 peak) ($P < 0.05$) vs NMHO patients. Body mass ($P < 0.05$), waist circumference ($P < 0.0001$), total and trunk fat mass ($P < 0.001$), systolic and diastolic BP ($P < 0.001$), fasting glucose ($P < 0.0001$), insulin sensitivity ($P < 0.05$), VO_2 peak and muscle endurance ($P < 0.0001$) were similarly improved in both groups after the program. Prevalence of NMHO was reduced by 17.91% ($P < 0.01$) after the program. Similar improvements in body composition, BP, and exercise parameters were found for MHO and NMHO men and women ($P < 0.05$). In all patients, improvement of VO_2 peak was negatively correlated with improvements in body composition, systolic blood pressure, and resting heart rate (HR) ($R = -0.61$ to -0.24; $P < 0.05$).

Conclusions: A long-term intensive lifestyle program including Mediterranean diet nutritional counselling and HIIT is an appropriate intervention in MHO and NMHO subjects with similar potential clinical health benefits including an improved body composition, BP, fasting glycemia, insulin sensitivity, VO_2 peak, and muscle endurance.

Résultats : Initialement, les patients OSSM avaient une pression artérielle (PA), une glycémie à jeun et des triglycérides plus bas, et un cholestérol-HDL et un prélèvement maximal d'oxygène (VO_2 max) plus élevé ($P < 0,05$) par rapport aux patients OSM. La masse corporelle ($P < 0,05$), le tour de taille ($P < 0,0001$), la masse grasse totale et tronculaire ($P < 0,001$), la PA systolique et diastolique ($P < 0,001$), la glycémie à jeun ($P < 0,0001$), l'insulinosensibilité ($P < 0,05$), la VO_2 max et l'endurance musculaire ($P < 0,0001$) s'étaient améliorés de façon similaire dans les deux groupes après le programme. La prévalence de sujets OSM a été réduite de 17,91 % ($P < 0,01$). Des améliorations similaires de la composition corporelle, de la PA et des paramètres d'effort ont été observées chez les hommes et les femmes OSSM et OSM ($P < 0,05$). Chez tous les patients, l'amélioration de la VO_2 max a été corrélée de manière négative avec les améliorations de la composition corporelle, de la pression artérielle systolique et de la fréquence cardiaque (FC) au repos ($R = -0,61$ à $-0,24$; $P < 0,05$).

Conclusions : Un programme intensif à long terme sur le mode de vie incluant des conseils nutritionnels sur la diète méditerranéenne et de l'EIHI est une intervention appropriée pour les sujets OSSM et OSM qui montre des avantages cliniques potentiels et similaires sur la santé dont l'amélioration de la composition corporelle, de la PA, de la glycémie à jeun, de l'insulinosensibilité, de la VO_2 max et de l'endurance musculaire.

indices.[14] We previously demonstrated that a 9-month program combining Mediterranean diet and high-intensity interval training (HIIT), was more effective at improving body composition, systolic blood pressure (SBP), and peak oxygen uptake (VO_2 peak)[15] relative to MICET in obese patients.[16,17] This work suggests that combining a Mediterranean diet approach with HIIT would provide an optimized program for improving body composition, cardiometabolic profile, and exercise parameters in obese subjects. In the present study, we assessed this possibility with a 9-month intensive lifestyle intervention.

Methods

Patients

This retrospective study was conducted at the cardiovascular prevention and rehabilitation centre of the Montreal Heart Institute and data from a 9-month intensive lifestyle modification program (Mediterranean diet nutrition counselling and high-intensity interval and resistance training) were analyzed (see the *Inclusion − Exclusion Criteria* section of the Supplementary Text). According to the Institutional Review Board policy of the Montreal Heart Institute concerning retrospective studies, the present study was approved by the Medical Director of the Montreal Heart Institute.

Measurements

All patients underwent a complete clinical evaluation including measurement of height, body mass, WC, body composition (Tanita, model 418 C), blood analysis, and maximal exercise test at baseline and 9 months[15] (see the *Measurements* section of the Supplemental Text for more details). Traditional CV risk factors considered were diabetes, hypertension, active smoking, and dyslipidemia as previously described.[15,16]

Definition of MHO and NMHO

Based on the criteria for the metabolic syndrome,[3] patients who met 0 or 1 of the criteria were classified as metabolically healthy. Consistent with previous literature on this topic,[3,4,18] the obesity criteria (fat mass percentage > 25% in men and > 35% in women) was excluded as a criterion, because our main purpose was to compare the effect of an intensive lifestyle modification program on cardiometabolic risk factors and functional capacity in MHO and NMHO patients. Other criteria used were: SBP $\geq$ 130 mm Hg or diastolic blood pressure (DBP) $\geq$ 85 mm Hg, fasting glycemia $\geq$ 5.6 mmol/L, triglycerides $\geq$ 1.70 mmol/L, high-density lipoprotein (HDL) cholesterol level < 1.0 mmol/L in men and < 1.3 mmol/L in women.[3,19] A total of 55 MHO and 79 NMHO patients were included from the entire sample (N = 134).

Intensive lifestyle intervention program

Supervised HIIT and resistance exercise consisted of 2 to 3 weekly 60-minute sessions. Subjects were encouraged to perform 1 to 2 additional unsupervised MICET sessions per week, such as walking and/or cycling (45-minute duration, Borg scale level of 12-14) outside or inside the centre.[15,17]

HIIT and resistance training program. HIIT prescription was based on the results of the baseline maximal treadmill exercise test and estimated maximal aerobic power and resistance training was prescribed as previously described[15,17] (see the *High-Intensity Interval Training and Resistance Training Program* section of the Supplemental Text for details).

Nutritional counselling intervention. All subjects underwent 5 individual meetings with a dietician in our centre. The first visit was used to obtain data on eating habits and motivation and provide the principles of the Mediterranean

Table 1. Anthropometric parameters before and after the intensive lifestyle intervention program in MHO and NMHO patients

	MHO (n = 55)		NMHO (n = 79)		
	Before	After	Before	After	*P*
Body mass, kg	95.7 ± 16.4	90.8 ± 16.4	97.2 ± 18.0	92.2 ± 17.1	a* b = 0.48 c = 0.99
BMI	35.8 ± 5.0	33.3 ± 6.4	36 ± 5.1	34.1 ± 4.7	a† b = 0.35 c = 0.96
WC, cm	109 ± 13	103 ± 13	112 ± 13	104 ± 17	a‡ b = 0.24 c = 0.81
Total fat mass, kg	40.4 ± 8.9	35.6 ± 9.8	40.9 ± 12.0	35.8 ± 10.2	a§ b = 0.80 c = 0.93
Fat mass percentage	42.2 ± 6.3	39.5 ± 7.4	41.7 ± 7.6	39.2 ± 7.5	a* b = 0.67 c = 0.88
Lean body mass, kg	55.4 ± 12.1	54.4 ± 12.2	56.6 ± 12.7	55.2 ± 11.9	a = 0.46 b = 0.53 c = 0.90
Trunk fat mass, kg	21.1 ± 4.7	18.7 ± 5.1	21.5 ± 5.6	19.0 ± 5.1	a§ b = 0.63 c = 0.99
Trunk fat mass percentage	41.1 ± 5.0	38.2 ± 6.5	40.9 ± 6.1	38.4 ± 6.3	a* b = 0.96 c = 0.81
RMR, kcal/d	1703 ± 358	1659 ± 359	1724 ± 425	1692 ± 358	a = 0.35 b = 0.47 c = 0.96

a, training effect; b, group effect; BMI, body mass index; c, interaction effect; MHO, metabolically healthy but obese; NMHO, metabolically unhealthy obese; RMR, resting metabolic rate; WC, waist circumference.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.0001$.

§ $P < 0.001$.

diet[15,17] (see the *Nutritional Counselling Intervention* section of the Supplemental Text for details).

Statistical analysis

All analyses were performed using StatView 5.0 (SAS Institute Inc) (see the *Statistical Analysis* section of the Supplemental Text for detailed statistical procedure).

Results

Baseline characteristics

Baseline characteristics for MHO and NMHO patients are described in detail in the Supplemental material (see the *Results* section of the Supplemental Text and Supplemental Table S1). Adherence to exercise training sessions (supervised and unsupervised sessions) was similar for both groups (MHO, 3.0 ± 1.1 vs NMHO, 2.7 ± 1.0 sessions per week; $P = 0.30$).

Anthropometric parameters

Anthropometric parameters before and after the program in MHO and NMHO patients are described in Table 1 and in the Supplementary Material (*Anthropometric Parameters* section of the Supplemental Text, and Supplemental Tables S2 and S3).

Blood parameters

Blood parameters before and after the program in MHO and NMHO patients are described in detail in the *Blood Parameters* section of the Supplemental Text, and in Supplemental Tables S4 and S5.

Exercise parameters

Exercise parameters before and after the program in MHO and NMHO patients are described in Table 2. At baseline, SBP, DBP, and resting HR were lower ($P < 0.05$), and maximal exercise capacity and HR recovery were higher ($P < 0.01$) in MHO vs NMHO patients. After the 9-months program, SBP and DBP were similarly reduced ($P < 0.001$) in both groups. Also, VO_2 peak, resting HR, and leg and abdominal muscle endurance were significantly improved in both groups ($P < 0.0001$). No interaction (group by program) ($P > 0.05$) was noted for exercise parameters. See the Supplementary Material for sex analysis and correlations (see the *Exercise Parameters* section of the Supplemental Text and Supplemental Tables S6 and S7).

Discussion

Major findings

The main findings of this study were that: (1) A longer-term intensive lifestyle intervention program combining

Table 2. Exercise parameters before and after the intensive lifestyle intervention program in MHO and NMHO patients

	MHO (n = 55)		NMHO (n = 79)		
	Before	After	Before	After	*P*
Resting SBP, mm Hg	127 ± 13	124 ± 12	137 ± 12	129 ± 12	a* b† c = 0.19
Resting DBP, mm Hg	80 ± 7	78 ± 6	83 ± 7	79 ± 6	a† b‡ c = 0.32
VO_2 peak, METs	8.75 ± 1.41	9.96 ± 1.52	8.08 ± 1.63	9.35 ± 1.91	a† b§ c = 0.90
Resting HR, beats per minute	73 ± 12	68 ± 11	78 ± 13	70 ± 10	a† b‡ c = 0.47
Maximal HR, beats per minute	162 ± 14	162 ± 14	158 ± 18	161 ± 17	a = 0.51 b = 0.26 c = 0.61
HR recovery at 1 minute	−26 ± 7	−27 ± 9	−22 ± 8	−23 ± 11	a = 0.45 b§ c = 0.94
Squat wall test, seconds	55 ± 37	128 ± 99	50 ± 41	121 ± 57	a† b = 0.44 c = 0.93
Shirado test, seconds	57 ± 41	110 ± 64	55 ± 39	109 ± 49	a† b = 0.78 c = 0.93

a, training effect; b, group effect; c, interaction effect; DBP, diastolic blood pressure; HR, heart rate; METs, metabolic equivalents; MHO, metabolically healthy but obese; NMHO, metabolically unhealthy obese; SBP, systolic blood pressure; VO_2, oxygen uptake.

* $P < 0.001$.

† $P < 0.0001$.

‡ $P < 0.05$.

§ $P < 0.01$.

Mediterranean diet nutritional counselling and HIIT similarly improved body composition (body mass, WC, total and trunk fat mass) in male and female MHO and NMHO patients. (2) Despite an initial better lipid profile (fasting glycemia, HDL cholesterol, and triglyceride level) in MHO patients, fasting glycemia and insulin resistance were similarly improved in both groups. (3) Despite initial better blood pressure, HR and VO_2 peak values (SBP, DBP, resting HR, HR recovery, and VO_2 peak) in MHO patients, blood pressure, resting HR, VO_2 peak (METs), and muscle endurance were similarly improved after the program in male and female MHO and NMHO patients. (4) The improvement in VO_2 peak (Δ METs) was inversely correlated with improvement of body composition in all patients, MHO and NMHO groups, and with fasting glycemia in the NMHO group only (Supplemental Table S7). To the best of our knowledge, this study is the first to document the effects of such a longer-term intensive lifestyle intervention program (9 months) on cardiometabolic and exercise parameters in MHO vs NMHO patients. Previous studies on lifestyle intervention in MHO and NMHO patients were often of shorter duration (3 to 6 months) using either a calorie-restricted diet alone,[5,6] or caloric restriction or MICET with cardiometabolic results pooled together.[8-10] Regarding exercise parameters, an improvement in VO_2 peak was reported only in 2 studies of female MHO subjects.[7,8]

Longer intensive lifestyle intervention program, and body composition parameters

In MHO patients, our results regarding improvement of body mass (−5 kg), WC (−6 cm), total (−4.8 kg), and trunk fat mass (−2.4 kg) (Table 1) were higher compared with 5 previous published studies[6-10] and similar to another.[5] More modest improvement in body mass (−1.2 to −4 kg), WC (0 to −5.6 cm), and total fat mass (−1.73 kg) were reported after either a calorie-restricted diet alone,[6,9] MICET alone,[7-9] or a calorie-restricted diet combined with MICET.[10] However, a 6-month calorie-restricted diet led to similar results (body mass, −5 kg; total fat mass, −3 kg) as ours in MHO women.[5] In NMHO patients, improvements in body mass (−5 kg), WC (−8 cm), total fat mass (−5.1 kg), and trunk fat mass (−2.5 kg) were higher than those observed in previous studies in obese patients using a HIIT intervention,[20,21] while being similar to previous studies from our group using the Mediterranean diet counselling and HIIT together.[15,17] However, improvements were less than those observed in a previous study using a more strictly controlled hypocaloric Mediterranean diet with interval training.[14] In our entire cohort, the prevalence of the metabolic syndrome was reduced by 18%, and 11% of the patients were reclassified as MHO, and 7% (9 patients) were no longer obese after the program. These data suggest that the combination of a Mediterranean diet with HIIT optimizes the improvement in body composition of male and female MHO and NMHO subjects and also helps to reduce the prevalence of the metabolic syndrome.

Obesity is associated with a higher relative risk of total and CV mortality and morbidity,[22-27] and NMHO patients are at higher risk for CVD, diabetes,[19,28,29] all-cause and CV mortality,[3,18,19,30] and cancer[3,30] compared with their nonobese counterparts. For MHO patients, conflicting studies report

either a similar relative risk for CVD,[28] diabetes,[29] and total CV and cancer mortality,[30] or a higher relative risk for CV events, and total CV and cancer mortality[3,18,31] compared with their nonobese counterparts (in models not adjusted for fitness). Improvements in body composition (ie, body fat mass and WC reductions) in obese patients were shown to reduce mortality,[27,32] and had numerous other health benefits (independently of MHO-NMHO status) on osteoarthritis, quality of life, physical functioning, cognition, and frailty.[33-35] However, recently, the LOOK-AHEAD (Action for Health in Diabetes) study, which combined drastic caloric restriction with MICET in obese patients with type 2 diabetes, did not demonstrate any reduction in CV morbidity or mortality.[36] However, an increase in WC and hemoglobin A1c and a decrease in VO_2 peak after the first year suggests a lack of long-term adherence to the intervention. The results of LOOK-AHEAD, although not surprising, should not be regarded as negative but should rather be used to optimize future trial design in obese patients (ie, low-carbohydrate Mediterranean diet and HIIT).

Longer intensive lifestyle intervention program and blood parameters

In MHO patients, we demonstrated a more favourable blood profile (fasting glycemia, HDL cholesterol, and triglyceride levels) compared with NMHO patients (Supplemental Table S4), as already reported by others.[3,6,9] Fasting glycemia and insulin sensitivity were also improved after the program in both groups. In MHO patients, this result is consistent with previous studies that reported an improved fasting glycemia after exercise training alone or caloric restriction[8-10] with no changes in other lipid parameters.[6,8-10] In NMHO patients, the improvement in fasting glycemia that we observed is concordant with previous studies using either exercise training alone[21] or a Mediterranean diet combined with exercise in patients with metabolic syndrome, and it is discordant with 2 previous studies from our group using the same intervention.[15,17] The fact that homeostatic model assessment of insulin resistance was similarly improved in our subgroup of MHO and NMHO patients by approximately 28%, is in agreement with 2 previous studies using exercise,[8,9] although other studies did not report such an improvement in MHO patients after exercise and diet,[10] or after caloric restriction in MHO and NMHO patients.[5,6] As noted by others, we did not observe any improvement in lipid parameters in MHO patients after the program.[6,8-10] This is presumably due to a better or more "normalized" initial lipid profile (higher HDL cholesterol and lower triglyceride levels) observed in our MHO patients. Regarding the NMHO group, a lack of improvement in the lipid profile after exercise alone,[20] exercise and/or calorie-restricted diet,[10] or an improvement in lipid profile after MICET and/or caloric restricted diet,[6,9,16,21] or a Mediterranean diet combined with intense exercise[14,15,17] has already been reported. These conflicting data are potentially due to: (1) the initially less favourable lipid profile of our group[15,17] as for another study,[14] and (2) the nature of the lifestyle intervention (diet or moderate exercise alone vs combined more intensive intervention). In patients not taking statins, similar results were found with an improved fasting glycemia after the program (Supplemental Table S5A). For patients taking statins, no improvement in blood parameters after the program were noted (Supplemental Table S5B).

Longer intensive lifestyle intervention program and exercise parameters

In MHO patients, we observed an initial higher VO_2 peak (METs), HR recovery, and lower resting HR and blood pressure compared with the NMHO group (Table 2). These results are in agreement with recent large cohort studies[3,37] that demonstrated a higher METs level and lower blood pressure in MHO patients, although previous studies with MHO classification based on insulin sensitivity did not note any difference.[9,38] To the best of our knowledge, our study is the first to document differences in HR variables between MHO and NMHO patients, because these parameters were not reported in previous exercise training studies.[8-10] The differences observed are probably due to the higher prevalence of impaired fasting glycemia and diabetes in NMHO patients (Supplemental Table S1) known to be responsible for autonomic control abnormalities.[39] Most importantly, we showed after our program that blood pressure, resting HR, VO_2 peak, and muscle endurance (abdominal and leg muscles) were similarly improved in both groups (Table 2). As well, we did observe similar improvements in exercise parameters when the groups of MHO and NMHO men and women with were analyzed separately (Supplemental Table S6). The METs improvement in MHO patients was greater (+1.21) than the one found by Arsenault et al.[8] (+0.34), but less than in the study of Roussel et al.[7] (+4.4), because the result of a difference in VO_2 peak measurement methods, was directly measured in those 2 studies but estimated in ours. However, exercise parameters were not reported in 2 other exercise training studies performed in MHO subjects.[9,10] Aerobic fitness and HR variables are very powerful independent predictors of total, CV mortality, and sudden death in men and women.[40-42] However, the level of fitness is lower in MHO and NMHO subjects compared with their nonobese counterparts.[3] As an example, an improvement of 1 METs (approximately +1.2 METs in our study) was shown to reduce total, CV mortality risk, and sudden death by 12%-22% in the general population.[40-42] How those benefits in prognosis could be applicable to our groups remains to be studied in future studies. As suggested by Ortega et al.,[3] VO_2 peak is an important protective parameter in MHO and NMHO patients. VO_2 peak improvement was moderately related to body composition improvement (especially fat mass) in all patients and obese phenotypes (Supplemental Table S7). However, whether improvement of body composition might also be related to adherence to a Mediterranean diet requires further study; these data were not collected in the present study. We also demonstrated a higher reduction of blood pressure in MHO and NMHO patients (SBP, −4 and −8 mm Hg) than previously observed in one study (SBP, −1.55 and −2 mm Hg),[9] and most studies found no improvement in blood pressure in MHO women.[7,8] In NMHO patients, discordant data concerning either a lack of change,[20] similar improvements to ours,[15,17] or higher improvements[7,14,21] (−10 and −18 mm Hg) in SBP were already reported. Certainly, blood pressure reduction in these cohorts

could potentially lead to clinical benefits, namely a lower incidence of CV events.

There are several limitations in our study including a non-randomized retrospective design of 1 single institution with no control group. The results may not be generalizable to all MHO and NMHO patients. Furthermore, data on adherence to the Mediterranean diet were not collected; the present study cannot assess whether diet and exercise training contributed equally to the cardiometabolic improvements observed. Finally, results might have also been influenced by changes to patient medication during the course of the study.

In conclusion, a longer-term intensive lifestyle intervention including Mediterranean diet nutritional counselling and HIIT improves to a similar degree body composition, blood pressure, fasting glycemia, insulin resistance, VO_2 peak, and muscle endurance in men, women, and MHO and NMHO patients. This study demonstrated the long-term feasibility and efficacy of an alternative and more intense lifestyle intervention in obese patients in clinical practice. Future larger, prospective, randomized control studies using similar interventions (Mediterranean diet and HIIT) are clearly warranted to allow generalization of our results to all MHO and NMHO patients and to verify whether such a program would have benefits with respect to CV morbidity and mortality.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2013.11.033.

SUPPLEMENTARY MATERIAL

Supplemental Text

Inclusion – exclusion criteria

Inclusion criteria at baseline were: age ≥ 18 years and obesity defined as: 1) waist circumference (WC) ≥80 cm for women, ≥94 cm for men and 2) fat mass percentage >25% in men and >35% in women [18]. Patients receiving pharmacological therapy for cardiovascular risk factors (i.e: hypertension, diabetes, dyslipidemia) were not excluded. Patients with a history of coronary heart disease (documented prior myocardial infarction, coronary revascularization, or myocardial ischemia on myocardial scintigraphy) were excluded. A total of 134 obese patients were included for the analysis. Only patients with complete baseline and 9-month data were included. Furthermore, to be included in the analysis, patients were required to perform a minimum of 2 supervised exercise sessions per week [15].

Measurements

A resting ECG, maximal exercise treadmill test using a ramp protocol, and a fasting blood test (glucose, insulin, lipid profile) were also performed [15, 16]. Insulin resistance was measured using the homeostasis model assessment-insulin resistance (HOMA-IR) = fasting insulin ($\mu U.ml^{-1}$) × fasting glucose ($mmol.l^{-1}$) / 22.5 [6]. During exercise testing, ECG and blood pressure were monitored continuously during exercise and 5-minute recovery. VO_2peak was defined as the highest level of METs achieved [15, 16]. All patients were instructed to take their usual medications prior to exercise testing. Patients also

performed an endurance test for abdominal and leg muscles (Shirado Test and squat wall test) [15]. Exercise training program attendance was obtained from medical charts and from an electronic system which automatically records each subject's entry into our centre. Weekly supervised exercise training sessions and physical activity performed in and/or out the center were reported in a diary.

High-intensity interval training and resistance training program

HIIT sessions were performed on an ergocycle (Precor, model 846i, USA) under supervision of a kinesiologist and consisted of a 5 min-warm up at 50 Watts, followed by two 10-minute sets of repeated bouts of 15 to 30 seconds at 80% of MAP interspersed by 15 to 30-second passive recovery periods, and a 5-min cool down at 50 watts [15, 17]. The targeted Borg rating of perceived exertion (RPE) was set at 15 during exercise sessions [15, 17]. The two 10-min periods were separated by a 4-min passive recovery. Total exercise time was 34 min per HIIT session [15, 17]. Resistance training (RT) was prescribed and performed under supervision of a kinesiologist. RT consisted of 20 minutes of circuit weight training performed with free weights and elastic bands adapted to each patient's capacity [15, 17]. For each muscle group, patients performed 1 set of 15 to 20 repetitions, followed by a 30-second rest period at a target RPE of 15 [15, 17].

Nutritional counseling intervention

The macronutrient composition (% of daily calories) of this diet was as follows: 20% protein, 45% carbohydrates (with a high intake of fiber), 35% fat (7% saturates, 25% monounsaturates, 2.5% polyunsaturates, ω6/ω3 ratio= 3-6). The total daily energy consumption was adapted to each patient, without severe restriction [15, 17]. The aim was to

meet, as far as possible, the Canadian guidelines (2000-2400 kcal/day). Subsequent visits at the 5^{th}, 12^{th}, 20^{th}, and 36^{th} weeks, were performed to review principles and adherence to the Mediterranean diet, to report dietary intake and to answer patients' questions. Additionally, participants received two group teaching sessions aiming at providing guidance regarding CV risk factor control, food labels and tasting Mediterranean-style dishes.

Statistical analysis

All data are expressed as mean ± standard deviation and/or in number and percentage. Normal distribution of the data was verified by a Shapiro-Wilk test. Data were logarithmically transformed when this assumption was not met. Normal adiposity subjects without metabolic syndrome (MetS), MHO and NMHO patient's prevalence was compared using a chi-square test before and after the program (supplementary materials: Table S2). For continuous variables, statistical differences in the MHO and NMHO groups were evaluated by a 2-way ANOVA (group and program) and by a 3-way ANOVA (program, group and gender) when responses by gender were performed (supplementary materials: Table S3, S6). To document the effects of VO_2peak improvement (Δ METs) on body composistion, fasting glycemia, BP and muscle endurance parameters, an ANCOVA was performed with group and program effects, and Δ METs added as a co-variable. A post hoc test (Bonnferoni) with a P value ≤ 0.05 was used to localize differences. Relationship between VO_2peak improvement (Δ METs) and cardiometabolic factor improvements (Δ values) in all patients, MHO and NMHO groups were performed using a Pearson coefficient of correlation (R).

Results

Baseline characteristics

Both groups were primarily composed of women (80 and 69%) with a BMI of approximately 35 $kg.m^{-2}$. There were no differences in baseline anthropometric parameters and prevalence of CV risk factors ($P>0.05$) except for impaired fasting glycemia and diabetes ($P<0.05$). Resting SBP and DBP were higher in NMHO patients ($P<0.05$).

Anthropometric parameters

There were no between-group differences at baseline regarding anthropometric parameters ($P>0.05$). After the 9 month-program, body mass was reduced by ~5 kg ($P<0.05$) and WC by ~ 7 cm ($P<0.0001$) in both groups. Similarly, total fat mass was reduced by ~5 kg and trunk fat mass by ~2.5 kg ($P<0.001$) in both groups. No interaction (group×program) effects ($P>0.05$) were noted for any anthropometric parameter. Prevalence of normal adiposity subjects without metabolic syndrome (MetS) and MHO patients were increased after the program (normal adiposity subjects: +6.71%, $P<0.01$; MHO: +11.19% $P<0.05$). Non-metabolically healthy obese patient's prevalence was reduced after the program (-17.91%, $P<0.01$, supplementary materials table S2). Similar improvements in body composition were found in MHO and NMHO men and women ($P<0.05$) and no gender × program interaction was noted (supplementary table S3). When VO_2peak improvement (Δ METs) was added as a covariable, the program effect was no longer statistically significant ($P>0.05$) for body mass, BMI, WC, total and trunk fat mass.

Blood parameters

As expected, baseline fasting glycemia and triglyceride level were lower while HDL-cholesterol was higher ($P<0.0001$) in MHO vs. MNHO patients. After the 9-month program, fasting glycemia was similarly reduced ($P<0.05$) in both groups. No interaction (group×program) ($P>0.05$) was noted for blood lipid parameters between groups. Fasting insulin was only available in a sub-group of 35 MHO and 30 NMHO patients for HOMA-IR determination. There was no initial difference in insulin resistance between groups ($P>0.05$) and HOMA-IR was similarly improved in both groups ($P<0.05$) (table S4). When analyzed by sex and group (MHO-NMHO), fasting glycemia was no more improved after the program ($P>0.05$, Table S3). In patients not taking statins, fasting glycemia was similarly improved in MHO and NMHO groups after the program (Table S5 A). In patients taking statins, blood parameters were not modified by the program (Table S5 B). When VO_2peak improvement (Δ METs) was added as a covariable, the program effect was no longer statistically significant ($P>0.05$) for fasting glycemia.

Exercise parameters

When analyzed by gender and group, similar improvements were noted for blood pressure, VO_2peak, resting HR and muscle endurance ($P<0.01$) in men and women with no gender × program interaction (supplementary materials table S6). VO_2peak improvement (Δ METs) was negatively correlated with improvements (Δ) in body mass, BMI, WC, total and trunk fat mass in all patients, in MHO and NMHO groups (R= -0.40

to -0.67, $P<0.05$; Table S7). In all patients, Δ METs was negatively correlated with improvements in SBP, resting HR and a trend was noted for fasting glycemia ($P=0.0508$). In the NMHO group, Δ METs was negatively correlated with improvements in fasting glycemia ($R=-0.34$, $P=0.0009$, Table S5). When Δ METs was added as a covariable, the program effect was no longer statistically significant ($P>0.05$) for resting HR and SBP but remained significant for DBP ($P<0.01$) and muscle endurance ($P<0.0001$).

Supplemental Table S1: Baseline characteristics of MHO and NMHO patients.

	MHO (n = 55)	**NMHO (n = 79)**
Age (years)	51.3 ± 8.7	54.1 ± 9.7
Male/female (n)	11/44	24/55
Height (cm)	165 ± 17	165 ± 13
Body mass (kg)	95.7 ± 16.4	97.2 ± 18.0
BMI (kg.m^{-2})	35.1 ± 5.2	35.7 ± 7.2
WC (cm)	109 ± 13	112 ± 13
Resting SBP (mmHg)	127 ± 13	137 ± 12 §
Resting DBP (mmHg)	80 ± 7	83 ± 7 *
Hypertension (*n* and %)	13 (23.6)	31 (39.2)
IFG (n and %)	1 (1.8)	33 (41) §
Diabetes (n and %)	1 (1.8)	10 (12) *
Dyslipidemia (*n* and %)	16 (29.1)	35 (44.3)
Smoking (*n* and %)	4 (7.3)	12 (15.2)
Medications (*n* and %)		
Antiplatelet agents	9 (16.4)	15 (19)
Beta-blockers	2 (3.6)	7 (8.9)
Calcium channel blockers	4 (7.3)	6 (7.6)
ACE inhibitors	3 (5.5)	10 (12.7)
Angiotensin receptor blocker	6 (10.9)	14 (17.7)
Hypoglycemic agent	2 (3.6)	2 (2.5)
Statins	13 (23.6)	20 (25.3)

BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure. IFG: impaired fasting glycemia ($\geq$ 5.6 $mmol.l^{-1}$), ACE: angiotensin converting ezyme ; *=$P<0.05$, §=$P<0.0001$.

Supplemental Table S2: Prevalence of normal adiposity subjects (with and without metabolic syndrome), metabolically healthy obese (MHO) and non-metabolically healthy obese (NMHO) patients before and after the intense lifestyle intervention program.

	Before	After	Difference	χ^2 P-value
Non obese subjects without MetS (n and %)	0 (0%)	9 (6.71)	+ 6.71 %	0.0022
Non obese subjects with MetS (n and %)	0 (0%)	0 (0%)	0	---------
MHO patients (n and %)	55 (41.04)	70 (52.23)	+ 11.19 %	0.0160
NMHO patients (n and %)	79 (58.95)	55 (41.04)	- 17.91 %	0.0033

MetS : metabolic syndrome, n=number, χ^2= chi-square.

Supplemental Table S3: Anthropometric parameters and fasting glycemia before and after the intensive lifestyle intervention program in MHO and NMHO men and women.

	MHO Men: n = 11 Women: n = 44		**NMHO** Men: n = 24 Women: n = 55		P-value
	Before	After	Before	After	
Body mass (kg)					a *
Men	113.3±16.5	105±16	108.5±19.2	103.3±18.1	b §
Women	91.2±13.2	86.7±14.1	92.2±15.1	87.3±14.2	c ns
					d ns
BMI (kg.m^{-2})					a †
Men	36.6±4.3	34±4	35.6±5.3	33.8±4.9	b ns
Women	34.7±4.4	32.7±4.7	35.7±5.7	33.5±5.1	c ns
					d ns
WC (cm)					a §
Men	120±11	110±11	119±12	107±24	b §
Women	106±11	100±12	108±11	103±11	c ns
					d ns
Total fat mass (kg)					a †
Men	37.5±9.3	31.6±9.9	37.3±10.7	32.7±10.0	b †
Women	41.1±8.7	36.7±9.5	42.5±12.5	37.3±10.0	c ns
					d ns
Fat mass percentage (%)					a †
Men	32.6±3.5	29.3±4.9	33.8±4.7	31.9±5.4	b §
Women	44.8±3.8	42.4±4.9	45.4±5.6	42.7±5.5	c ns
					d ns
Trunk fat mass (kg)					a †
Men	22.6±5.5	19.4±5.9	21.7±4.6	19.6±5.8	b ns
Women	20.7±4.4	18.4±4.9	21.3±6.0	18.7±4.8	c ns
					d ns
Trunk FM percentage (%)					a †
Men	35.7±3.9	40.4±5.6	36.2±3.7	34.3±5.6	b §
Women	42.4±4.2	39.9±5.5	43.0±5.9	40.4±5.6	c ns
					d ns
Fasting glucose (mmol/L)					a ns
Men	4.87±0.53	5.04±0.35	5.97±1.03	5.55±0.51	b ns
Women	4.97±0.50	4.79±0.35	5.77±1.02	5.50±0.67	c §
					d ns

a= program effect, b= gender effect, c= MHO-NMHO effect, d= interaction effect (gender × program), * =P<0.05, † =P<0.01, ‡ P<0.001, §=P<0.0001, ns=not significant.

Supplemental Table S4: Blood parameters before and after the intensive lifestyle intervention program in MHO and NMHO patients.

	MHO (n=55)		NMHO (n=79)		p-value
	Before	After	Before	After	
Fasting glucose (mmol.l^{-1})	4.95 ± 0.51	4.85 ± 0.36	5.83 ± 1.03	5.52 ± 0 .63	a* b§ c=0.23
HOMA-IR $^{\&}$	4.00 ± 2.22	3.07 ± 1.82	3.22 ± 2.89	2.39 ± 1.18	a* b=0.053 c=0.88
Total cholesterol (mmol.l^{-1})	5.15 ± 0.95	4.96 ± 0.85	4.94 ± 1.13	4.73 ± 1.10	a=0.13 b=0.09 c=0.94
HDL-cholesterol (mmol.l^{-1})	1.50 ± 0.28	1.52 ± 0.23	1.16 ± 0.26	1.21 ± 0.28	a=0.31 b§ c=0.56
LDL-cholesterol (mmol.l^{-1})	3.16 ± 0.83	2.97 ± 0.81	3.02 ± 0.97	2.86 ± 0.98	a=0.12 b=0.29 c=0.87
Triglycerides (mmol.l^{-1})	1.07 ± 0.34	1.01 ± 0.45	1.68 ± 0.66	1.49 ± 0.66	a=0.07 b§ c=0.33
Triglycerides/HDL	0.75 ± 0.29	0.69 ± 0.33	1.55 ± 0.77	1.33 ± 0.80	a=0.08 b§ c=0.32

HDL: high-density lipoprotein, LDL: low-density lipoprotein. a = training effect, b = group effect, c=interaction effect, * = P<0.05, § = P<0.0001. HOMA-IR: homeostasis model assessment-insulin resistance, & = data available only in 35 MHO and 30 NMHO patients.

Supplemental Table S5 A and B: Blood analysis parameters before and after the intensive lifestyle intervention program in MHO and NMHO without (A) and with (B) statins use.

Without statins (A)	**MHO (n=42)**		**NMHO (n=59)**		p-value
	Before	After	Before	After	
Fasting glucose (mmol.l^{-1})	5.01±0.51	4.83±0.34	5.70±0.98	5.45±0.59	a^{*} $b^{\S}$ c^{ns}
Total cholesterol (mmol.l^{-1})	5.02±0.92	4.92±0.85	5.27±1.06	4.97±1.05	a^{ns} b^{ns} c^{ns}
HDL-cholesterol (mmol.l^{-1})	1.53±0.28	1.53±0.23	1.18±0.24	1.23±0.28	a^{ns} $b^{\S}$ c^{ns}
LDL-cholesterol (mmol.l^{-1})	3.01±0.73	2.87±0.76	3.31±0.87	3.07±0.91	a^{ns} b^{*} c^{ns}
Triglycerides (mmol.l^{-1})	1.06±0.36	1.07±0.48	1.70±0.69	1.49±0.65	a^{ns} $b^{\S}$ c^{ns}
Triglycerides/HDL	0.72±0.31	0.72±0.35	1.51±0.79	1.29±0.74	a^{ns} $b^{\S}$ c^{ns}

With statins (B)	MHO (n=13)		NMHO (n=20)		p-value
	Before	After	Before	After	
Fasting glucose (mmol.l^{-1})	4.76±0.45	4.87±0.44	6.22±1.07	5.72±0.72	a^{ns} $b^{\S}$ c^{ns}
Total cholesterol (mmol.l^{-1})	5.54±0.96	5.08±0.84	3.95±0.69	3.96±0.87	a^{ns} $b^{\S}$ c^{ns}
HDL-cholesterol (mmol.l^{-1})	1.41±0.22	1.46±0.23	1.05±0.27	1.17±0.27	a^{ns} $b^{\S}$ c^{ns}
LDL-cholesterol (mmol.l^{-1})	3.63±0.98	3.25±0.90	2.16±0.69	2.19±0.87	a^{ns} $b^{\S}$ c^{ns}
Triglycerides (mmol.l^{-1})	1.10±0.20	0.80±0.17	1.61±0.54	1.45±0.70	a^{ns} $b^{\S}$ c^{ns}
Triglycerides/HDL	0.81±0.23	0.56±0.15	1.63±0.70	1.43±0.98	a^{ns} $b^{\S}$ c^{ns}

a= program effect, b= MHO-NMHO effect, c= interaction effect (group × program), *=P<0.05, §=P<0.0001, ns=not significant.

Supplemental Table S6: Exercise parameters before and after the intensive lifestyle intervention program in MHO and NMHO men and women.

	MHO Men: n = 11 Women: n = 44		**NMHO** Men: n = 24 Women: n = 55		P-value
	Before	After	Before	After	
Resting SBP (mmHg)					a†
Men	131±10	129±12	143±111	133±12	b‡
Women	126±13	122±11	133±11	127±11	c§
					d ns
Resting DBP (mmHg)					a†
Men	81±9	81±7	83±6	79±4	b*
Women	79±7	76±5	82±7	78±6	c ns
					d ns
VO_2peak (METs)					a§
Men	9.70±1.12	11.47±1.83	8.93±1.99	10.34±2.10	b§
Women	8.49±1.36	9.5±1.07	7.71±1.28	8.88±1.61	c‡
					d ns
Resting HR (bpm)					a†
Men	70±17	66±13	74±13	70±11	b ns
Women	73±10	68±10	79±12	70±10	c*
					d ns
Squat wall test (sec.)					a§
Men	76±44	180±167	83±56	140±62	b§
Women	49±32	111±59	35±19	112±52	c ns
					d ns
Shrirado (sec.)					a§
Men	89±62	163±86	79±51	130±61	b§
Women	47±26	92±44	44±25	98±37	c ns
					d ns

a= program effect, b= gender effect, c= MHO-NMHO effect, d= interaction effect (gender × program), * =P<0.05, † =P<0.01, ‡ P<0.001, §=P<0.0001, ns=not significant.

Supplemental Table S7: Relationship between VO_2peak improvement (Δ METs) and cardiometabolic factors improvements (Δ values) in all patients, MHO and NMHO groups.

	All patients	**MHO**	**NMHO**
	Δ METs	**Δ METs**	**Δ METs**
Δ resting SBP	R= - 0.29, P=0.028	R= - 0.31, P=0.076	R= - 0.17, P=0.240
Δ resting HR	R= - 0.24, P=0.032	R= - 0.33, P=0.061	R= - 0.19, P=0.204
Δ Glycemia	R= - 0.20, P=0.0508	R= 0.03, P=0.858	R= - 0.34, P=0.009
Δ Body mass	R= - 0.61, P<0.0001	R= - 0.56, P=0.0002	R= - 0.67, P<0.0001
Δ BMI	R= - 0.58, P<0.0001	R= - 0.61, P<0.0001	R= - 0.56, P<0.0001
Δ WC	R= - 0.44, P<0.0001	R= - 0.40, P=0.011	R= - 0.50, P<0.0001
Δ Total FM	R= - 0.60, P<0.0001	R= - 0.58, P<0.0001	R= - 0.62, P<0.0001
Δ Trunk FM	R= - 0.53, P<0.0001	R= - 0.57, P<0.0001	R= - 0.48, P=0.0002

Δ = delta, Δ values were calculated by subtracting the 9 months value with the baseline one.