



Intensive lifestyle intervention including high-intensity interval training program improves insulin resistance and fasting plasma glucose in obese patients [☆]

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ABSTRACT

Objectives. To analyze the effects of a long-term intensive lifestyle intervention including high-intensity interval training (HIIT) and Mediterranean diet (MedD) counseling on glycemic control parameters, insulin resistance and β -cell function in obese subjects.

Methods. The glycemic control parameters (fasting plasma glucose, glycated hemoglobin), insulin resistance, and β -cell function of 72 obese subjects (54 women; mean age = 53 ± 9 years) were assessed at baseline and upon completion of a 9-month intensive lifestyle intervention program conducted at the cardiovascular prevention and rehabilitation center of the Montreal Heart Institute, from 2009 to 2012. The program included 2–3 weekly supervised exercise training sessions (HIIT and resistance exercise), combined to MedD counseling.

Results. Fasting plasma glucose (FPG) (mmol/L) (before: 5.5 ± 0.9 ; after: 5.2 ± 0.6 ; $P < 0.0001$), fasting insulin (pmol/L) (before: 98 ± 57 ; after: 82 ± 43 ; $P = 0.003$), and insulin resistance, as assessed by the HOMA-IR score (before: 3.6 ± 2.5 ; after: 2.8 ± 1.6 ; $P = 0.0008$) significantly improved, but not HbA1c (%) (before: 5.72 ± 0.55 ; after: 5.69 ± 0.39 ; $P = 0.448$), nor β -cell function (HOMA- β , %) (before: 149 ± 78 ; after: 144 ± 75 ; $P = 0.58$).

Conclusion. Following a 9-month intensive lifestyle intervention combining HIIT and MedD counseling, obese subjects experienced significant improvements of FPG and insulin resistance. This is the first study to expose the effects of a long-term program combining HIIT and MedD on glycemic control parameters among obese subjects.

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Introduction

Lifestyle modifications refer to an integrated non-pharmacological approach aiming to reduce traditional cardiovascular risk factors. Current practice guidelines recommend integrated lifestyle modifications including weight control, exercise training, and nutritional modifications to improve cardiovascular risk factors and to promote health (Eckel et al., 2014; Haskell et al., 2007). Clinical research has so far mainly focused on the single components of lifestyle interventions (diet,

exercise) to assess their respective effects on health (Estruch et al., 2013; Manson et al., 2002), despite the fact that they are recommended in combination (Eckel et al., 2014; Haskell et al., 2007). More recently, however, few randomized trials have tested them in combination (Fernandez et al., 2012; Group, T.L.A.R., 2013; Landaeta-Díaz et al., 2013).

Mediterranean diet (MedD) alone has been shown to reduce the incidence of major cardiovascular events and to be very effective in the reduction and long-term maintenance of body mass, blood pressure, and cholesterol levels in obese subjects with high cardiovascular risk (Estruch et al., 2013; Shai et al., 2008). High-intensity interval training (HIIT) involves bouts of exercise at an intensity close to 90–100% of VO_2 max, interspersed with periods of active or passive recovery. The advised exercise modality in the most recent guidelines is generally moderate-to-vigorous intensity continuous exercise training (MICET), (Donnelly et al., 2009; Eckel et al., 2014; Haskell et al., 2007; Jensen et al., 2014) and very little details regarding HIIT protocols available are provided (Eckel et al., 2014; Haskell et al., 2007). Previous studies demonstrated that HIIT was more efficient to improve body composition, blood pressure, lipid composition, and VO_2 peak than MICET

Acronyms: CAD, coronary artery disease; FPG, fasting plasma glucose; HIIT, high-intensity interval training; IFG, impaired fasting glycemia; MedD, Mediterranean diet; MICET, moderate-to-vigorous intensity continuous exercise training.

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(Drigny et al., 2013; Gremeaux et al., 2012; Helgerud et al., 2007; Tjønnå et al., 2008). In addition, short-term studies (12 weeks) have shown that MedD combined with HIIT was superior to MedD alone to improve fitness, body composition, circulating endothelial progenitors, and health-related quality of life (Fernandez et al., 2012; Landaeta-Díaz et al., 2013), indicating a cumulative effect of both nutritional and exercise interventions.

Even among non-diabetic subjects, glycated hemoglobin (HbA_{1c}) is a strong predictor of hard coronary events in the general population (Pai et al., 2013), which makes glycemic control parameters interesting targets in primary prevention. Previous short-term randomized trials studies (12 to 16 week follow-ups) comparing HIIT vs. MICET have demonstrated either similar improvements of glycemic control parameters (fasting glycemia and insulin resistance), (Mitranun et al., 2014; Nybo et al., 2010) or superiority of HIIT for improvements of glycemic control parameters in overweight/obese patients (Mitranun et al., 2014; Tjønnå et al., 2008). The effects of a long-term combination of HIIT with MedD on glycemic parameters are currently not documented in obese patients.

The first objective of this study was to assess the cumulative effects of HIIT and MedD in a long-term (9 months) lifestyle intervention program on glycemic control parameters, insulin resistance and β -cell function in obese subjects. The second objective was to describe the effects of this program on the same parameters in obese subjects according to their initial glycemic and insulin sensitivity statuses (diabetes, impaired fasting glycemia [IFG] or normal glycemia; insulin sensitive or resistant).

Methods

A retrospective study was performed at the Cardiovascular Prevention and Rehabilitation Center (ÉPIC) of the Montreal Heart Institute. Data from patients undergoing a 9-month clinical intensive lifestyle modification program (2009–2012), involving supervised HIIT training and MedD nutrition counseling, were retrospectively analyzed. According to the Institutional Review Board policy of the Montreal Heart Institute concerning retrospective studies, the present study was approved by the Ethical Committee of the Montreal Heart Institute.

Study population

Inclusion criteria at baseline were age over 18 years, and obesity defined as: 1) waist circumference ≥ 80 cm for women, ≥ 94 cm for men and 2) fat mass percentage $>25\%$ in men and $>35\%$ in women (Cornier et al., 2011). Detailed inclusion and exclusion criteria are provided in the Supplementary Methods section.

Exercise training program

Supervised exercise training sessions consisted of 2 to 3 supervised 60-min weekly sessions of HIIT (combined with resistance training). HIIT prescription was based upon the results of the baseline maximal treadmill exercise test and estimated maximal aerobic power. HIIT sessions were performed on ergocycle (Precor, model 846i, USA) under supervision of a kinesiologist and consisted of a 5-min warm-up at 50 W, followed by two sets of 10 min of repeated bouts of 15 to 30 s at 80% of maximal aerobic power interspersed by 15 to 30 s periods of passive recovery, and a 5-min cool down at 50 W. The targeted Borg rating of perceived exertion (RPE) was set at 15 during the exercise sessions. The two 10-min periods were separated by a 4-min passive recovery. Total exercise time was 34 min per HIIT session. Resistance training was prescribed and performed under supervision of a kinesiologist, and consisted of 20 min of circuit weight training performed with free weights and elastic bands adapted to each patient's capacity. For each muscle group, patients performed 1 set of 15 to 20 repetitions, followed by a 30-s rest period, at a target RPE of 15. Subjects were

encouraged to perform 1 or 2 additional unsupervised continuous moderate intensity sessions per week, such as walking and/or cycling (45-min duration, Borg scale level averaging 12–14) outside or inside the center.

Nutritional counseling intervention

All subjects underwent 5 individual meetings with a dietician in our center. The first visit was used to obtain data on eating habits and motivation, and to provide the principles of the MedD. Details of the nutritional counseling are exposed in the Supplementary Methods section.

Statistical analysis

Statistical analysis was performed with SPSS[®] Statistics 20.0 (IBM[®], Armonk, NY). Continuous variables are expressed as mean \pm standard-deviation. Categorical variables are expressed as frequencies (percentage). For continuous variables, statistical differences in all subjects were evaluated by an ANOVA with repeated measure (time). Statistical differences in the sub-groups of obese subjects (insulin resistant and sensitive; diabetics, IFG and normal fasting plasma glucose [FPG]) were evaluated by a 2 way ANOVA (group and program). A post hoc test (Bonferroni) with a P value ≤ 0.05 was used to localize differences. Insulin resistance was defined as an HOMA-IR score ≥ 2.6 (Ascaso et al., 2003).

Results

Baseline characteristics

Baseline characteristics are shown in Table 1. Seventy-two obese subjects were included, from 2009 to 2012. Forty-three subjects (59%) had a normal FPG (<5.6 mmol/L), twenty-two subjects (30%) had an IFG (FPG: 5.6–6.9 mmol/L) and seven subjects were diabetics (FPG ≥ 7.0 mmol/L). Insulin resistance (HOMA-IR ≥ 2.6) was present in 41 subjects (57%).

Table 1

Baseline characteristics of the obese subjects.

Age (years) (mean \pm SD)	53 \pm 9
Gender (female/male)	(54/18)
Body mass (kg) (mean \pm SD)	97 \pm 18
Body mass index (kg/m ²) (mean \pm SD)	35.3 \pm 5.3
Waist circumference (cm) (mean \pm SD)	111 \pm 13
Total fat mass (kg) (mean \pm SD)	41 \pm 11
Trunk fat mass (kg) (mean \pm SD)	21 \pm 5
Diabetes	7 (10%)
Hypertension	22 (31%)
Current smoking	4 (6%)
Dyslipidemia	26 (36%)
VO ₂ peak (METs) (mean \pm SD)	8.6 \pm 1.6
Total cholesterol (mmol/L) (mean \pm SD)	5.0 \pm 1.1
LDL-cholesterol (mmol/L) (mean \pm SD)	3.0 \pm 1.0
HDL-cholesterol (mmol/L) (mean \pm SD)	1.4 \pm 0.3
Triglycerides (mmol/L) (mean \pm SD)	1.4 \pm 0.7
Medication	
Antiplatelet agents	14 (19%)
Beta-blockers	5 (6.9%)
Calcium channel blockers	6 (8.3%)
ACE inhibitors	7 (9.7%)
Angiotensin receptor blocker	16 (22%)
Statins	20 (27%)
Oral antidiabetic	3 (4%)
Parenteral insulin	0 (0%)

FPG: fasting plasma glucose; HOMA-IR: Homeostasis Model Assessment for insulin resistance; SD: standard-deviation.

Study conducted at the EPIC Center of the Montreal Heart Institute (2009–2012).

Glycemic control and insulin parameters

After the program, 2 subjects were diabetics (reduction of 5 subjects or 7%; $P = 0.08$), 15 subjects had an IFG (reduction of 7 subjects or 9.7%; $P = 0.18$) and 55 subjects had a normal fasting glycemia (increase of 12 subjects or + 16.6%; $P = 0.03$). After the program, insulin resistance was present in 32 subjects (44%) indicating a reduction in 12 patients (− 13%) ($P = 0.06$). Glycemic control and insulin parameters for all obese subjects are presented in Table 2.

Glycemic control and insulin parameters for insulin resistant and insulin sensitive obese subjects are presented in Table 3. At baseline, glycemic and insulin parameters (FPG, HbA_{1c}, fasting insulin, HOMA-IR), and beta-cell function (HOMA-β) were higher in insulin resistant obese subjects ($P < 0.001$). After the program, FPG, fasting insulin and insulin resistance (HOMA-IR) were significantly improved only in insulin resistant obese subjects, and no improvement was seen for insulin sensitive obese subjects.

Body composition, blood pressure and exercise parameters

Improvements of body composition, blood pressure and exercise parameters are provided in supplementary materials (Tables S1 to S4).

Discussion

In our study, we report the effects of a long-term intensive lifestyle intervention program, including HIIT and MedD counseling, on glycemic control parameters in obese subjects. Our results show that an improvement of the FPG, fasting insulin, and HOMA-IR occurs upon completion of the program, but only for obese subjects with baseline insulin resistance. These results highlight a possible role for this combined lifestyle intervention in the improvement of risk factors of cardiovascular diseases in the obese population.

The combination of MedD and HIIT have only been studied by one group so far, in a 12 week program involving 45 patients (Fernandez et al., 2012; Landaeta-Díaz et al., 2013). They showed that compared to MedD alone, the combination improves the levels of circulating of endothelial progenitor cells, cardiorespiratory fitness, cardiovascular risk factors, and health-related quality of life. To date, no study aimed to identify the effects of this combination on the glycemic control parameters and insulin resistance as a primary objective. Additionally, no report of the long-term effects of this combination on health-related parameters has been published. Our study thus constitutes the second report of the effects of this combination on health parameters, and the first one with a relatively long-term program (9 months). In the context of the endemic state of obesity in Western countries, these results are relevant in a public health perspective, given that an obese phenotype, independently of the other cardiovascular risk factors, increases the risks of cardiovascular diseases, CAD, death from CAD, congestive heart failure, and diabetes (Hubert et al., 1983; Wilson et al., 2007).

The Look AHEAD investigators previously showed that among overweight-to-obese diabetic patients, an intensive lifestyle intervention including a caloric-restriction diet and regular MICET, with the aim

of a 7% weight loss or more, is associated with a modest increase in partial remission of diabetes (Gregg et al., 2012), and an improvement of health-related quality of life (Williamson et al., 2009). More recently, however, they failed to show an improvement of major cardiovascular events rates (compared to the control group) after a median follow-up of 9.6 years (Group, T.L.A.R., 2013). However, by the time this trial was initiated, the benefits of the MedD and HIIT were not as well established compared to other modes of nutritional and exercise training, respectively.

It has recently been shown in a randomized trial that a MedD adds a protection against major cardiovascular events in high-risk patients without known cardiovascular disease compared to a control low-fat diet (Estruch et al., 2013). MedD improves fasting plasma glucose and insulin resistance compared to a low-fat, restricted-calorie diet in diabetic patients (Shai et al., 2008). However, it is not associated with significant improvements of fasting plasma glucose and insulin sensitivity in non-diabetic subjects (Shai et al., 2008). Complementary lifestyle interventions, such as exercise training, should thus be encouraged to address the improvement of glycemic parameters in non-diabetic patients, in the objective of reducing coronary events (Pai et al., 2013). In the last decade, growing evidence has made HIIT to be considered as a safe and effective alternative to MICE in a variety of settings. It has a better tolerability profile, and improves further peak VO₂ (Gayda et al., 2012; Guiraud et al., 2011; Meyer et al., 2010; Rognum et al., 2004; Weston et al., 2014). Short-term HIIT programs have been assessed in very small cohorts, and have been shown to improve glycemic control parameters (Adams, 2013). However, the benefits of a long-term HIIT program in the improvement of glycemic control in obese patients has only scarcely been studied (Tjønnå et al., 2008). This drove the rationale for our observational study.

It could be hypothesized that designing a study similar to the Look AHEAD trial, but involving HIIT and MedD instead of MICET and a caloric-restriction diet, might improve cardiovascular outcomes, but it should be investigated (Group, T.L.A.R., 2013). The results of our study and of others (Fernandez et al., 2012; Gregg et al., 2012; Landaeta-Díaz et al., 2013; Pai et al., 2013) could constitute a rationale for designing a randomized controlled trial analyzing the effects of a combination of HIIT and MedD on glycemic control parameters and cardiovascular clinical outcomes.

Limitations and strengths

The main limitation of our study, explained by its retrospective nature, is the absence of comparative assessment of the combination of MedD and HIIT to groups of patients undergoing different lifestyle interventions. It hinders any attempt to extrapolate the superiority of this specific combination of lifestyle intervention over another lifestyle intervention, a shortcoming we are fully conscious about. The aim was however to provide relevant exploratory hypothesis-generating data by testing this specific combination of lifestyle interventions. The effects of a long-term program involving the combination of MedD and HIIT on glycemic control parameters in obese patients have never been investigated before. It is of clinical value to know if benefits can be sustained over a long period, particularly with obese subjects. Many examples in the primary prevention literature have shown that short-term benefits of lifestyle interventions are not sustained in the long-term. In addition, the effects of this longer-term combined intervention on glycemic control and insulin resistance status has never been studied. It is of great clinical value to know if patients with different glycemic and/or insulin resistance statuses respond similarly or differently to this combined long-term intervention, and this is the main originality of this work. Given the scarcity of studies assessing an integrated lifestyle modification approach on health-related endpoints, even though lifestyle modifications are recommended in combination in guidelines, our study could contribute to provide hypothesis-generating data on the

Table 2

Glycemic control, insulin parameters and β-cell function in all obese subjects before and after the program.

All subjects (n = 72)	Before	After	Δ	ANOVA P-value
FPG (mmol/L)	5.5 ± 0.9	5.2 ± 0.6	−0.31 ± 0.64	<0.0001
HbA _{1c} (%)	5.72 ± 0.55	5.69 ± 0.39	−0.03 ± 0.34	0.448
Insulin (pmol/L)	98 ± 57	82 ± 43	−16 ± 44	0.003
HOMA-IR	3.6 ± 2.5	2.8 ± 1.6	−0.8 ± 2.0	0.0008
HOMA-β (%)	149 ± 78	144 ± 75	−5 ± 71	0.58

FPG: fasting plasma glucose, HOMA-β: Homeostasis Model Assessment for β-cell function, HOMA-IR: Homeostasis Model Assessment for insulin resistance.

Study conducted at the EPIC Center of the Montreal Heart Institute (2009–2012).

Table 3Glycemic control, insulin parameters and β -cell function in insulin sensitive and resistant obese subjects before and after the program.

	Insulin sensitive (n = 31)			Insulin resistant (n = 41)			P value
	Before	After	Δ	Before	After	Δ	
FPG (mmol/L)	5.0 \pm 0.5	4.9 \pm 0.4	-0.1 \pm 0.4	6.0 \pm 1.0	5.5 \pm 0.7**	-0.5 \pm 0.7	a < 0.0001 b = 0.020 c = 0.101
HbA _{1c} (%)	5.43 \pm 0.30	5.48 \pm 0.27	+0.07 \pm 0.28	5.94 \pm 0.60	5.76 \pm 0.42	-0.11 \pm 0.37	a < 0.0001 b = 0.394 c = 0.130
Insulin (pmol/L)	54 \pm 14	58 \pm 22	+4 \pm 21	132 \pm 54	100 \pm 46*	-31 \pm 50	a < 0.0001 b = 0.045 c = 0.008
HOMA-IR	1.7 \pm 0.4	1.8 \pm 0.8	+0.1 \pm 0.7	5.1 \pm 2.5	3.5 \pm 1.6*	-1.57 \pm 2.38	a < 0.0001 b = 0.010 c = 0.002
HOMA- β (%)	120 \pm 76	129 \pm 63	+8 \pm 74	171 \pm 74	156 \pm 82	-15 \pm 68	a = 0.002 b = 0.805 c = 0.361

FPG, fasting plasma glucose; HOMA- β , Homeostasis Model Assessment for β -cell function; HOMA-IR, Homeostasis Model Assessment for insulin resistance. a = group effect, b = program effect, c = interaction effect (group \times program).

Insulin resistance was defined by a HOMA-IR \geq 2.6. a = group effect, b = program effect, c = interaction effect (group \times program).

Study conducted at the EPIC Center of the Montreal Heart Institute (2009–2012).

* Before vs. after post hoc Bonferroni test: $P < 0.001$.

** Before vs. after post hoc Bonferroni test: $P < 0.0001$.

combination of nutritional and exercise programs, and puts grounds for future outcome-oriented prospective trials on this topic.

Another limitation is that our study includes a relatively low sample size, and may not have been powered enough to detect improvements of HbA_{1c}.

The external validity of our study is limited by three main elements. First, the enrolment in the program was not free for the subjects, thus our data can only be extrapolated to people in the population who can afford to pay for a lifestyle intervention, who may carry a different cardiovascular risk burden profile compared to the general population. Second, the enrolment in the program requires a certain degree of motivation, given that recruitment was made on a self-initiative basis. This limitation, however, applies to the majority of lifestyle intervention studies, given that non-motivated subjects usually do not enroll in such trials, and this shortcoming does not thwart the scope of our findings. Third, the exclusion of subjects who did not complete the program, for whom we did not have the final data on the glycemic control parameters, causes a selection bias.

We used a surrogate marker of insulin resistance (HOMA-IR) instead of a direct measure with an oral glucose tolerance test (OGTT). This study used data from a clinical program not originally designed for research purposes, which explains the lack of systematic measures of OGTT upon inclusion of the patients. Also, no adherence data for the MedD is available, but the purpose of the study was to assess the effects of a program on an intent-to-treat basis.

The originality of our study resides in the fact that we analyzed a long-term program, compared to previous attempts to assess the effects of HIIT on glycemic control parameters, that a combined lifestyle intervention was used, and that the glycemic control parameters improvements have never been assessed previously following such intervention in obese subjects.

Conclusion

In conclusion, we showed that a 9-month intensive lifestyle intervention including HIIT and MedD improves FPG, fasting insulin, and insulin sensitivity, particularly among insulin resistant obese subjects. Our data suggest that these lifestyle interventions might improve cardiovascular risk factors in obese subjects, and calls for the implementation of a randomized trial analyzing the combination of HIIT and MedD on hard cardiovascular endpoints.

Conflict of interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.pmedr.2015.04.015>.

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