Low intensity endurance exercise targeted for lipid oxidation improves body composition and insulin sensitivity in patients with the metabolic syndrome

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SUMMARY

Background: To investigate the effects of individualized training on the metabolic syndrome.

Methods: Twenty-eight patients, suffering from the metabolic syndrome were studied before and after 2 months of training and compared to eleven patients who did not follow any training. All the patients were overweight. Training was individualized at the point where fat oxidation was maximal (LIPOX$_{max}$) as determined by calorimetry.

Results: The patients exhibited a significant reduction in body weight (-2.6 ± 0.7 kg; $P = 0.002$), fat mass (-1.55 ± 0.5 kg; $P = 0.009$), waist (-3.53 ± 1.3cm; $P < 0.05$) and hip (-2.21 ± 0.9cm; $P < 0.05$) circumferences, and improved the ability to oxidize lipids at exercise (crossover point: $+31.7 \pm 5.8$ W; $P < 0.0001$; LIPOX$_{max}$: $+23.5 \pm 5.6$ W; $P < 0.0001$; lipid oxidation: $+68.5 \pm 15.4$ mg·min^{-1}; $P = 0.0001$). No clear improvement in either lipid parameters or fibrinogen were observed.

The surrogates of insulin sensitivity evidenced a decrease in insulin resistance: HOMA%S (software): $+72.93 \pm 32.64$; $p < 0.05$; HOMA-IR (simplified formula): -2.42 ± 1.07; $P < 0.05$; QUICKI: $+0.02 \pm 0.004$; $P < 0.01$; SI = 40/I: $+3.28 \pm 1.5$; $P < 0.05$.

Significant correlations were found between changes in body weight and HOMA-IR and between changes in LIPOX$_{max}$ and QUICKI.

Conclusions: Individualized aerobic training improves lipid oxidation, body composition and insulin resistance.

Key-words: Insulin resistance · Exercise training · Lipid oxidation · Crossover concept.

RÉSUMÉ

Amélioration de la composition corporelle et de la sensibilité à l'insuline chez des patients atteints du syndrome métabolique après un réentraînement à faible intensité ciblant l'oxydation lipidique

Objectif : Analyser les effets d'un réentraînement individualisé sur les composantes du syndrome métabolique.

Méthodes : 28 patients ayant les caractéristiques du syndrome métabolique ont été explorés avant et après 2 mois d'entraînement et comparés à 11 patients non réentraînés. Tous les patients étaient en surpoids. L'intensité de l'entraînement correspondait au niveau d'oxydation maximale des lipides (LIPOX$_{max}$) déterminée par calorimétrie.

Résultats : On observe une diminution du poids (-2.6 ± 0.7 kg ; $P = 0.002$), de la masse grasse (-1.55 ± 0.5 kg ; $P = 0.009$), du tour de taille (-3.53 ± 1.3 cm ; $P < 0.05$) et du tour de hanche (-2.21 ± 0.9 cm ; $P < 0,05$), et une amélioration de la capacité à oxyder les lipides à l'exercice (point de croisement : $+31.7 \pm 5.8$ W ; $P < 0.0001$; LIPOX$_{max}$: $+23.5 \pm 5.6$ W ; $P < 0.0001$; oxydation lipidique : $+68.5 \pm 15.4$ mg·min^{-1} ; $P = 0.0001$). Aucune amélioration n'a été observée au niveau des paramètres lipidiques et du fibrinogène.

On observe une diminution de la résistance à l'insuline : HOMA%S (logiciel) : $+72.93 \pm 32.64$; $p < 0.05$; HOMA-IR (formule simplifiée): -2.42 ± 1.07 ; $P < 0.05$; QUICKI : $+0.02 \pm 0.004$; $P < 0.01$; SI = 40/I : $+3.28 \pm 1.5$; $P < 0.05$.

Des corrélations significatives apparaissent entre l'évolution du poids et de HOMA-IR et entre l'évolution du LIPOX$_{max}$ et de QUICKI.

Conclusions : Un entraînement aérobie individualisé améliore conjointement l'oxydation lipidique, la composition corporelle et la sensibilité à l'insuline.

Mots-clés : Résistance à l'insuline · Entraînement · Oxydation lipidique · Crossover concept.

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*E*xercise training has proven its efficiency as a preventive treatment for type 2 diabetes (Non Insulin Dependent Diabetes Mellitus NIDDM) in patients with impaired glucose tolerance [1, 2].

Consistent with a large body of evidence [3] showing that sedentarity promotes a worsening of the insulin resistance syndrome while exercise is able to counteract this process, well-conducted randomized studies have thus given a clear demonstration that exercise is a major therapeutic tool against the metabolic syndrome.

However, exercise prescription remains poorly codified and protocols differ among investigators. For example, intensity was set at the anaerobic threshold [4] at 50% of maximal heart rate [5], 40% or 70% of predetermined VO_{2max} [6] or resistance training [7]. Exercise prescription was thus based only on theoretical assumptions. There was no attempt to ascertain whether the level that was applied was actually the best for promoting lipid oxidation.

However, exercise calorimetry [8] makes it possible to define such a level and has thus been proposed for improving exercise prescription.

In precedent studies, we compared CHO and lipid oxidation rates in overweight subjects and matched lean controls at various exercise intensities to examine the balance of substrate utilization during exercise [9]. The submaximal exercise test we used allowed the determination of two parameters representative of the balance of substrate oxidation: the crossover point (defined as the power at which energy predominantly derives from CHO) and the maximal fat oxidation rate point ($LIPOX_{max}$). These two points can be hypothesized to be helpful to prescribe exercise training and to individualize it.

Accordingly, in this study, we investigated the effects of such a targeted training in patients with the metabolic syndrome. Our working hypothesis was that targeted exercise training would decrease fat mass and increase insulin sensitivity via its effects on lipid oxidation during exercise.

Patients and methods

Patients

Twenty-eight patients, suffering from the metabolic syndrome as defined with the clinical criteria (see below), who went to our unit for a nutritional and metabolic check-up and to follow a training session, were recruited and compared to eleven patients who did not follow any training.

All the patients were overweight (Body Mass Index BMI > 25) or obese (BMI ≥ 30.0).

No patients had diabetes-related complications, and no medications were administered.

Subjects were excluded if they had ischemic heart disease or other medical conditions for which the prescribed exercise might be contraindicated.

Before the training session, subjects did not spend more than 2 h/wk in sports activities and had no physically demanding job.

The World Health Organisation (WHO) metabolic syndrome

The diagnosis of the metabolic syndrome was done according to the definition proposed by the WHO expert committee [10-12], slighly modified since we did not assess insulin sensitivity with the glucose clamp but with the homeostatic model assessment.

Patients were classified as insulin resistant if they presented at least either insulin resistance and/or impaired glucose regulation and in addition two or more of the other components.

Insulin resistance was defined by value of insulin sensitivity in the lowest quartile. Impaired glucose regulation was defined as fasting plasma glucose ≥ 6.1 mmol.l^{-1}.

The other components of the syndrome were raised arterial blood pressure defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, raised plasma triglycerides ≥ 1.7 mmol.l^{-1} and/or HDL cholesterol < 0.9 mmol.l^{-1} for men, < 1.0 mmol.l^{-1} for women, waist to hip ratio > 0.9 for men, > 0.85 for women and/or BMI > 30kg.m^{-2} and urinary albumin excretion rate ≥ 20 mg·min^{-1}.

Anthropometry

Height and weight measurements were performed. Body composition (Body Mass Index and Body Fat) was assessed with a multifrequency bioelectrical impedancemeter (Dietosystem Human IM Scan) that uses low intensity (100-800 µA) at the following frequencies: 1, 5, 10, 50, and 100 kHz. Analysis was performed with the software Master 1.0 that gives the choice among 25 published equations for body composition calculations (body water, fat mass...) [13, 14].

The body mass index was calculated as weight in kilograms divided by height in squared meters (kg.m^{-2}).

Waist and hip circumference were taken with the subjects in a standing position and waist-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

Physical characteristics are indicated in *Table I*.

Method

Experimental design

The overweight insulin-resistant patient participated in an exercise-training intervention of 8 wk. The second group, made up of eleven overweight patient, served as a nontraining C group. Measurements were made before the start of the exercise-training program and repeated within 2 wk after 8 wk of exercise training.

Table I
Subjects characteristics before and after the training period in the training group (T) and in the control group (C).

	T		C	
	Before	**After**	**Before**	**After**
	n = 28		**n = 11**	
Sex ratio (F/M)	21/7		7/4	
Age, yr	52.04 ± 2.40		52.73 ± 3.44	
Height, cm	163.09 ± 1.9		163 ± 3.77	
Body weight, kg	85.54 ± 3.58	$82.94 \pm 3.43**$	89.01 ± 6.98	88.04 ± 6.15
BMI, $kg.m^{-2}$	32 ± 1.7	$31.03 \pm 1.02**$	33.89 ± 2.57	33.31 ± 2.43
Body fat, kg	35.75 ± 2.1	$33.5 \pm 1.94**$	43.66 ± 7.97	37.62 ± 4.88
Fat Free Mass, kg	49.44 ± 2.46	49.02 ± 2.36	50.73 ± 6.64	50.39 ± 3.67
Waist, cm	99 ± 3.83	$94.8 \pm 3.53*$	101.4 ± 7.89	102.4 ± 5.27
Hip, cm	112.85 ± 2.5	$111.5 \pm 2.56*$	115 ± 7.72	112.4 ± 6.2
WHR	0.88 ± 0.03	0.85 ± 0.03	0.88 ± 0.05	0.91 ± 0.03
VO_{2max}, $mL.kg.min^{-1}$	17.21 ± 1.17	$20.94 \pm 1.25**$	19.95 ± 3.27	20.1 ± 3.3

Values are expressed as mean $\pm$ S.E.M. n = number of subjects. F = female. M = male. BMI = Body Mass Index. WHR = Waist-hip ratio. *$p < 0.05$. **$p < 0.01$ after *vs* before training.

Exercise testing

The test consisted on a three-minutes warm-up at 20% of theoretical maximal power (W_{max}), followed by four six-minutes steady-states workloads at 30, 40, 50 and 60% of theoretical W_{max}, using the protocol described previously [9].

All subjects came after an overnight fast (i.e., 12 h). No dietary restriction was imposed during the days before exercise testing. A cannula was inserted in the cephalic vein at the level of the cubital fossa for blood sampling at rest.

The results of this test were used to determine the exercise training intensity.

Exercise training

The exercise training program (group T) consisted of cycling on an ergometer (Ergoline Bosh 500) for forty minutes. Subjects trained during 8 wk, three times per week. Heart rate was monitored continuously during the training sessions (Polar Cardiometer, Monitor, France). Training was performed at the level of maximal lipid oxidation defined by exercise calorimetry (see below). For all patients, the beginning of the training sessions took place at the laboratory under the supervision of a professional instructor, and the patients were then advised to continue training at home according to the procedure which had been defined in our unit.

Materials

The patients performed each test on the same electro-magnetically braked cycle ergometer (Ergoline Bosh 500). Heart rate was monitored continuously throughout the test by standard 12-lead procedures. Gas volumes (airflow, O_2 and CO_2 concentrations) in inspired and expired air were measured with a digital computer based breath to breath exercise analyzing system (CPX Medical Graphics, Mineapolis, Minnesota, USA) with a mouthpiece and nose clip system.

Calculations

VO_{2max}

VO_{2max} *(Tab I)* was calculated by using Astrand nomograms which were included in a home-made software.

Substrate oxidation balance

Indirect calorimetric measurements were performed to determine whole body substrate oxidation. For each six-minutes steady-states, the last 3 min were used to collect expiratory gas by an adaptation to a nose clip and a mouth piece. Calculation of CHO and lipid oxidation rates was assessed from this gas exchange measurements according to the non-protein respiratory quotient (R) technique [15]. VO_2 and VCO_2 were determined as the mean of measurements during the fifth and sixth min of each state, according to Mac Rae [16].

As we describe in a previous study [9], we determined two parameters representative of the balance between fat and CHO utilization: the first parameter is the crossover point (COP) of substrate oxidation and was expressed as a percentage of the theoretical maximal working capacity calculated according to Wasserman's equations [17]. This point corresponding at the power at which energy from CHO-derived fuels predominates over energy from lipids. This

power intensity is thus employed here as a standardized index of substrate balance at exercise.

The second parameter is the maximal fat oxidation point (LIPOX$_{max}$) [9], also expressed as a percentage of the theoretical maximal working capacity, and corresponding to the exercise intensity at which the highest rate of fat oxidation was observed. This power was used to set the intensity of the training program.

Lipid rate oxidation

Lipid rate oxidation was calculated from gas exchange measurements by using nonprotein RER values, according to the following equations [15]:

Lipid Rate Oxidation (mg·min^{-1}) = 1.6946 VO$_2$-1.7012 VCO$_2$

with mass expressed in milligrams per minute and gas volume in milliliter per minute.

VO$_2$ and VCO$_2$ were determined as the average of measurements when LIPOX$_{max}$ was obtained. These equations are based on the assumption that protein breakdown contributes little to energy metabolism during exercise [18].

Surrogates of insulin resistance

The homeostasis model assessment insulin resistance index (HOMA-IR) and insulin sensitivity (HOMA%S) were calculated with a computer-solved model [19] and with the simplified formula [20]:

HOMA-IR = insulinemia $\times$ glycemia/22.5

with glycemia expressed in micromoles per liter.

The insulin sensitivity check index (QUICKI) was calculated with the formula [21]:

QUICKI = 1/(log insulinemia + log glycemia)

with glycemia expressed in milligrams per deciliter.

The simplified evaluation of insulin sensitivity based upon its reciprocal relationship with baseline insulin ("SI = 40/I") was calculated with the formula [22, 23]:

SI = 40/insulinemia

with SI units expressed in min^{-1}/(μU/ml) $\times$ 10^{-4}.

Biochemical analysis

All samples were assayed for glucose, insulin and lipids with routine well-standardized procedures.

Plasma insulin was assayed by the Bi-Insulin IRMA kit (ERIA-Diagnostics Pasteur, France) which does not cross-react with proinsulin. Plasma glucose was determined with a Vitros Product Chemistry analyzer (Johnson & Johnson, Clinical Diagnostics, Rochester, NY, USA).

Statistics

Data are presented as mean $\pm$ S.E.M. All statistical analyses were performed using a commercial software package (SigmaStat, version 1.0, Jandel Corporation, USA). The normality of the samples was checked with the Kolmogorov-Smirnov test which evidenced a lack of normality for most parameters. Accordingly, we employed non-parametric

tests. Signed rank tests (Wilcoxon) were performed to compare various parameters before and after the 8-wk exercise program. In order to evaluate the relationship among various parameters, Spearman correlation analysis were performed.

P < 0.05 was considered to be statistically significant.

Results

Baseline characteristics of subjects

Subjects description corresponding to the metabolic syndrome defined by the World Health Organisation (WHO).

The homeostasis model assessment insulin resistance index (HOMA-IR) calculated with a simplified formula indicates that subjects are insulin resistant with an average value of 5.44 (mean normal values in 147 non-diabetic lean and obese subjects tested in our laboratory: HOMA-IR = 2.02 + 0.123; lowest limit of the upper quartile: 3.03; when the HOMA%S is calculated with the software, control values are 121.6 + 3.77 i.e., the upper limit of the lowest quartile is 90.8).

HOMA-IR appears to be correct for predicting the value obtained with the computer-solved model (HOMA%S). There was a reciprocal relationship between both surrogates (r = 0.98; p < 0.01) corresponding to

HOMA%S = 13.8 + 167.1/HOMA-IR

Concordance of the HOMA%S obtained from HOMA-IR with this equation and that obtained with the software, as assessed by the Bland-Altman difference plot, was satisfactory (estimated mean difference 0.07; 95% confidence interval: – 5 to + 5).

Accordingly, there is no statistically significant difference between HOMA%S value obtained with the computer-solved model and HOMA%S predicted with this formula. There was also a good correlation between HOMA%S and the QUICKI (r = 0.96). Actually, the correlation was even better with the index SI = 40/I (r = 0.98).

The waist-hip ratio (WHR) was correlated with the HOMA-IR and also with 1/HOMA%S.

Both waist circumference and hip circumference were negatively correlated with VO$_{2max}$. Their WHR was also negatively correlated with VO$_{2max}$.

There was a correlation between the rate of lipid oxidation at the level of the LIPOX$_{max}$ and the fat free mass. The beta-cell responsiveness (HOMA%B) calculated with the software was correlated with the body mass index. All the correlations are presented in *Table II*.

Effects of training

Anthropometry

Physical characteristics of the subjects are presented in *Table I*. There were no significant differences among groups for age, height, body weight and BMI before the intervention.

Table II

Linear correlations among anthropometric, ergometric and metabolic parameters calculated on the whole sample of subjects before training.

Correlations	r	p
Hip (cm) and VO_{2max} (ml.kg.min^{-1})	− 0.42	0.03
Waist (cm) and VO_{2max} (ml.kg.min^{-1})	− 0.60	0.0015
WHR and VO_{2max} (ml.kg.min^{-1})	− 0.57	0.003
WHR and HOMA-IR	0.57	0.015
WHR and 1/HOMA%S	0.53	0.025
Lipid oxidation (mg·min^{-1}) and Fat Free Mass (kg)	0.43	0.03
HOMA%B and BMI (kg·m^{-2})	0.49	0.013

The changes in body composition for the two groups are shown in *Table I*.

The exercise training resulted in a significant reduction in body weight for the group T (− 2.6 ± 0.7 kg; P = 0.002), BMI (− 0.96 ± 0.2kg.m^{-2}; P = 0.003) and body fat (− 1.55 ± 0.5kg; P = 0.009). By contrast, there was no change in lean body mass (49.44 ± 2.46 *vs* 49.02 ± 2.36 kg, P > 0.05).

Waist and hip circumferences decreased significantly (− 3.53 ± 1.3 cm; P < 0.05 and − 2.21 ± 0.9 cm; P < 0.05) but the waist-hip ratio was not significantly changed.

VO_{2max} increased significantly (+ 3.1 ± 0.8 ml.kg.min^{-1}; p = 0.001).

No change was observed for the group C for these parameters during the two months.

Substrate oxidation

The various parameters of substrate utilization were modified with the training program *(Fig 1)*.

The COP of substrate utilization increased significantly in the group T after training (31.46 ± 3.7 *vs* 52.75 ± 4.4%; P < 0.0001). The point of maximal fat oxidation rate was shifted also significantly towards higher power intensities after training in group T (27.7 ± 2.3 *vs* 44.8 ± 3.7%; P < 0.0001). The rate of fat oxidation obtained at the LI-POX$_{max}$ increased significantly after training in group T (122.4 ± 16.3 *vs* 186.63 ± 17.6 mg·min^{-1}; P = 0.0001). No significant change was observed in the control group (P > 0.05) *(Fig 1)*.

Biochemical analyses

Plasma glucose concentrations and resting plasma insulin concentrations did not differ between after and before training *(Tab III)*.

Lipid profile and hemostasis parameters did not significantly improve *(Tab III)*.

Surrogates of insulin resistance

The surrogate measurements of insulin resistance changed significantly *(Fig 2)*.

The software-derived (J Levy, version 2.00 [19]) homeostasis model assessment index "HOMA%S" increased significantly (before: 100 ± 25.5 after: 175 ± 44.9; p < 0.05) and the simpler "HOMA-IR = Insulin × glucose/22.5" decreased (before: 5.44 ± 1.78 after: 2.82 ± 0.74; p < 0.05).

The insulin sensitivity check index (QUICKI) increased significantly (before: 0.27 ± 0.01 after: 0.29 ± 0.01; p < 0.001) as well as the simplified evaluation of insulin sensitivity calculated with the formula SI = 40/I (before: 4.62 ± 1.16 after: 7.99 ± 2.05; p < 0.05).

Correlations among improvements due to the training session

When trained and untrained subjects are considered together we find a negative correlation between the change in body weight and the change in HOMA-IR (r = − 0.44, p = 0.04), and a correlation between the change in insulin sensitivity (QUICKI) and the LIPOX$_{max}$ (r = 0.54, p = 0.03).

Discussion

The goal of this study was to investigate the effect of targeted training at a working intensity corresponding to the LIPOX$_{max}$ on body composition and fuel metabolism.

Our results show that this targeted exercise training protocol markedly improves the ability to oxidize lipids at exercise. Besides, it improves body composition, with a reduction in fat mass, waist circumference and hip circumference. Despite no clear improvement in either lipid parameters or fibrinogen, the most usual surrogates of insulin sensitivity as well as the software-derived evaluation of insulin sensitivity by the homeostasis model assessment (HOMA) evidences a decrease in insulin resistance.

Whether the patients had actually performed training at home was confirmed by the increase in VO_{2max}. In this study, we indirectly calculated this parameter from the linear correlations between heart rate and work loads at steady state during the submaximal steps of our exercise protocol. Such a procedure, which is less reliable than the direct measurement of VO_{2max} during a short progressively increasing maximal exercise protocol, was employed here for three reasons. First, it was easy to obtain during our specific exercise-test designed to perform exercise calorimetry. On the other hand, given the duration of this test, standard conditions would not be fulfilled if a final attempt to reach a maximal level were done and the actual VO_{2max} would be underestimated. Finally, in these subjects who were markedly sedentary, a maximal stress, in our experience, is a rather harmful event which is frequently perceived as very unpleasant, so that most subjects would discontinue the protocol. By contrast, the submaximal workloads were not so harmful and the subjects always agreed with the proposal to repeat the test after training in order to verify the efficacy of training.

In fact, this simplistic measurement should be rather considered as a marker of training or sedentarity than a mea-
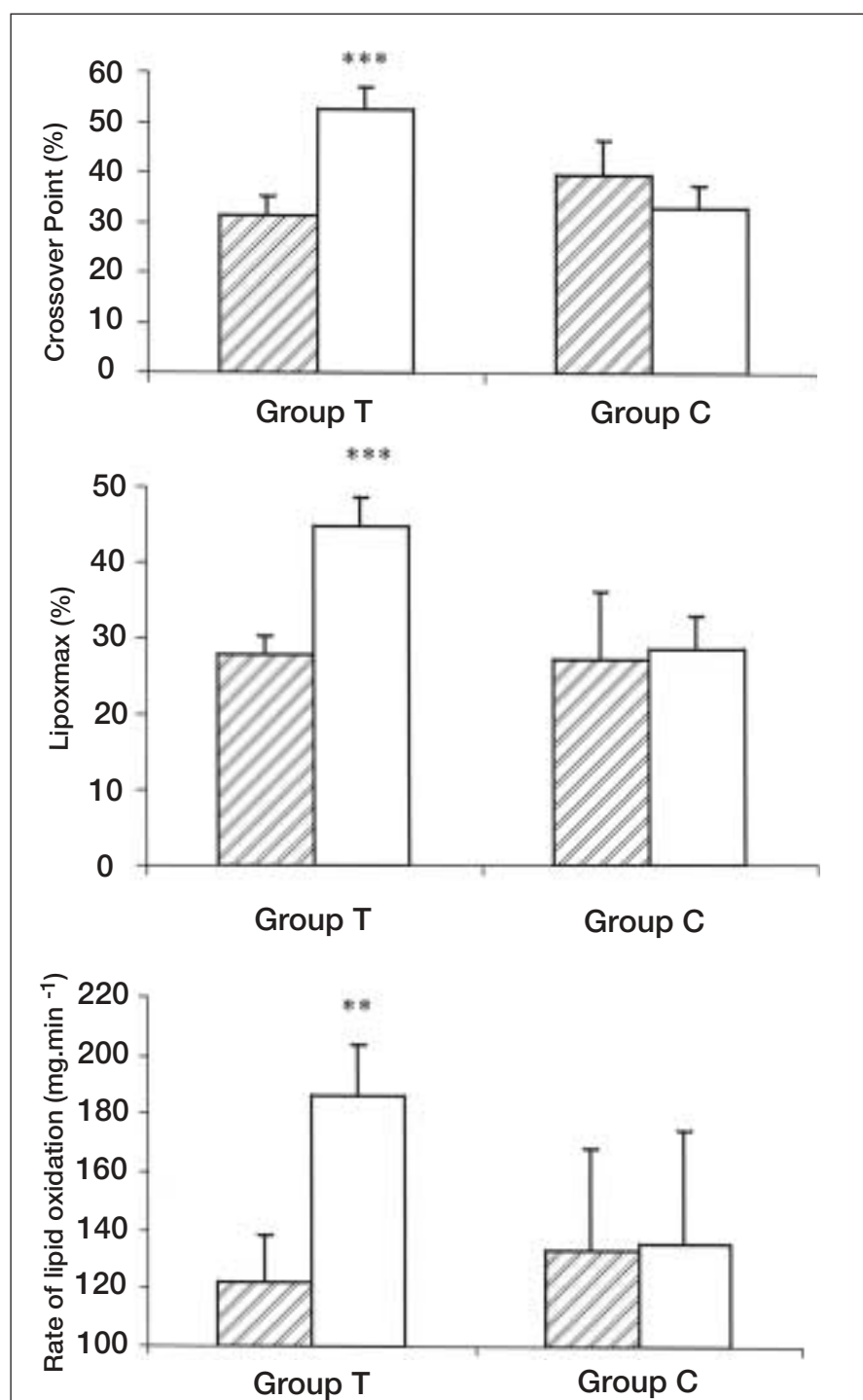
Figure 1

Crossover point, LIPOX$_{max}$ (both of them expressed as percentages of the theoretical maximal working capacity) and rate of lipid oxidation at LIPOX$_{max}$ before training session (hatched bars) and after training session (open bars) in trained (group T) and control groups (group C). Values are expressed as mean ± S.E.M.; ** $p<0.001$; *** $p<0.0001$ after vs before training. There was no significant difference between the two groups for values observed before training.

surement of aerobic working capacity. In our subgroup of trained patients, it is found to increase very significantly. In the whole group, it exhibits a negative correlation with the waist circumference which indicates that sedentarity is associated with an increase in abdominal fat mass.

Actually, the exercise testing, in this protocol, was designed to measure the ability to oxidize lipids at various levels of exercise. The methodological aspects of this procedure have been extensively discussed in a previous paper [9]. With this test, we evidenced a highly significant increase in the ability to oxidize lipids, which is both shifted towards higher exercise intensity levels and increased in terms of crude oxidation rate. Our working hypothesis is that such a measurement will help to ascertain whether the training procedure employed by the patient has actually improved lipid oxidation. In addition, this verification after training makes it

Table III
Biochemical analyses.

	T		C	
	Before	**After**	**Before**	**After**
Plasma glucose conc., mmol.L^{-1}	6.23 ± 0.75	5.54 ± 0.35	6.34 ± 0.92	7.13 ± 0.77
Plasma insulin conc., µU/mL	17.88 ± 5.26	10.45 ± 2	15.5 ± 2.56	10.4 ± 1.45
Total cholesterol, g·L^{-1}	2.13 ± 0.1	2.17 ± 0.09	2.27 ± 0.25	2.29 ± 0.08
HDL-cholesterol, g·L^{-1}	0.57 ± 0.05	0.58 ± 0.05	0.38 ± 0.02	0.46 ± 0.04
LDL-cholesterol, g·L^{-1}	1.24 ± 0.08	1.31 ± 0.09	1.59 ± 0.1	1.45 ± 0.16
Triglycerides, g·L^{-1}	1.35 ± 0.21	1.34 ± 0.21	1.94 ± 0.41	1.82 ± 0.40
Fibrinogen, g·L^{-1}	3.56 ± 0.22	3.6 ± 0.2	3.83 ± 0.42	3.84 ± 0.47
PAI$_1$ bioactive, µg/ml	19.73 ± 3.05	25.45 ± 2.83	21.67 ± 4.84	15.5 ± 1.2
PAI$_1$ antigen, µg/ml	85.5 ± 16.5	83.6 ± 25.68	98.5 ± 19.5	117.67 ± 25.01

PAI$_1$ = Plasminogen Activator- Inhibitor − 1. Values are expressed as mean ± S.E.M.

possible to re-target the training protocol in the expectance to increase its further efficiency.

This study is not randomized, but includes a group of subjects who could not or did not want to train themselves. As shown on *Table I*, this second group is well matched with the trained group. Although a selection bias cannot theoretically be ruled out, it is clear that, in these subjects, none of the improvements evidenced in the training group can be found. We thus believe that, although non randomized, this study strongly suggests that the effects we observe are due to training and do not occur when the patient remains sedentary.

Since the goal of the study was to develop a training protocol for treating insulin resistance, we included some measurements of the parameters of the metabolic syndrome. However, on the whole, the improvements that can be evidenced after these two initial months of training are rather moderate, contrasting with the marked changes in exercise calorimetry.

Concerning insulin sensitivity itself, we did not include a heavy procedure such as the glucose clamp or the minimal model but the measurement of baseline insulin and glucose allowed us to calculate some of the usual surrogates of insulin sensitivity measurements. The accuracy of these measurements requires some comments. Although some of them have become very popular and are employed widely without any caution, it is clear that these surrogates are valid only within certain limits which are not always taken into account by most investigators [22, 24]. To summarize briefly all these discussions, surrogates are valid only when the beta-cell is able to increase baseline insulin levels for compensating insulin resistance. Any situation which disturbs this compensatory feedback results in a loss of validity of the surrogates. This is the case for situations of high insulin sensitivity (athletes, patients suffering from reactive hypoglyce-

mia), but also growth hormone deficiency, antiprotease-treated HIV-patients, pubertal children. Even in the case of overt non insulin dependent diabetes mellitus, despite their wide use, these surrogates are questionable [22]. In a study on American Indians included in the Strong Heart Study it has been shown that below the cut-off value of 126 mg·dl^{-1} the HOMA-IR fairly predicts insulin sensitivity while above this value it becomes totally irrelevant [25].

In fact, obese patients with only mild alterations of glucose homeostasis such as those included in our protocol, represent a situation where the surrogates have been repeatedly demonstrated to reflect rather well the more sophisticated measurements of insulin sensitivity. Given the fact that the strongest prediction of insulin resistance was actually insulin itself, we recently proposed in this case an even more simplistic surrogate SI = 40/Ib (where SI is insulin sensitivity and Ib basal insulin) which has the advantage to be expressed in dose-response units of glucose disposal for insulin (min^{-1}/ (µU/ml) × 10^{-4}) and thus predicts minimal model measurements [23]. All these surrogates, including SI = 40/Ib, have been demonstrated to be valid in populations like that of this study.

On the whole, all the surrogates evidence an overall increase in insulin sensitivity after training, while this parameter is not improved in the control group. Interestingly, despite their strong reciprocal correlation, the software-derived HOMA%S and the formula-derived HOMA-IR do not exactly provide the same result, and, for instance, the correlation of insulin resistance with the waist-to-hip ratio is slightly more significant when insulin resistance is calculated with the software. This is consistent with the statement of the promoters of this approach that some information is lost with the simplified formula and that the full modeling calculation gives a better assessment of insulin sensitivity.
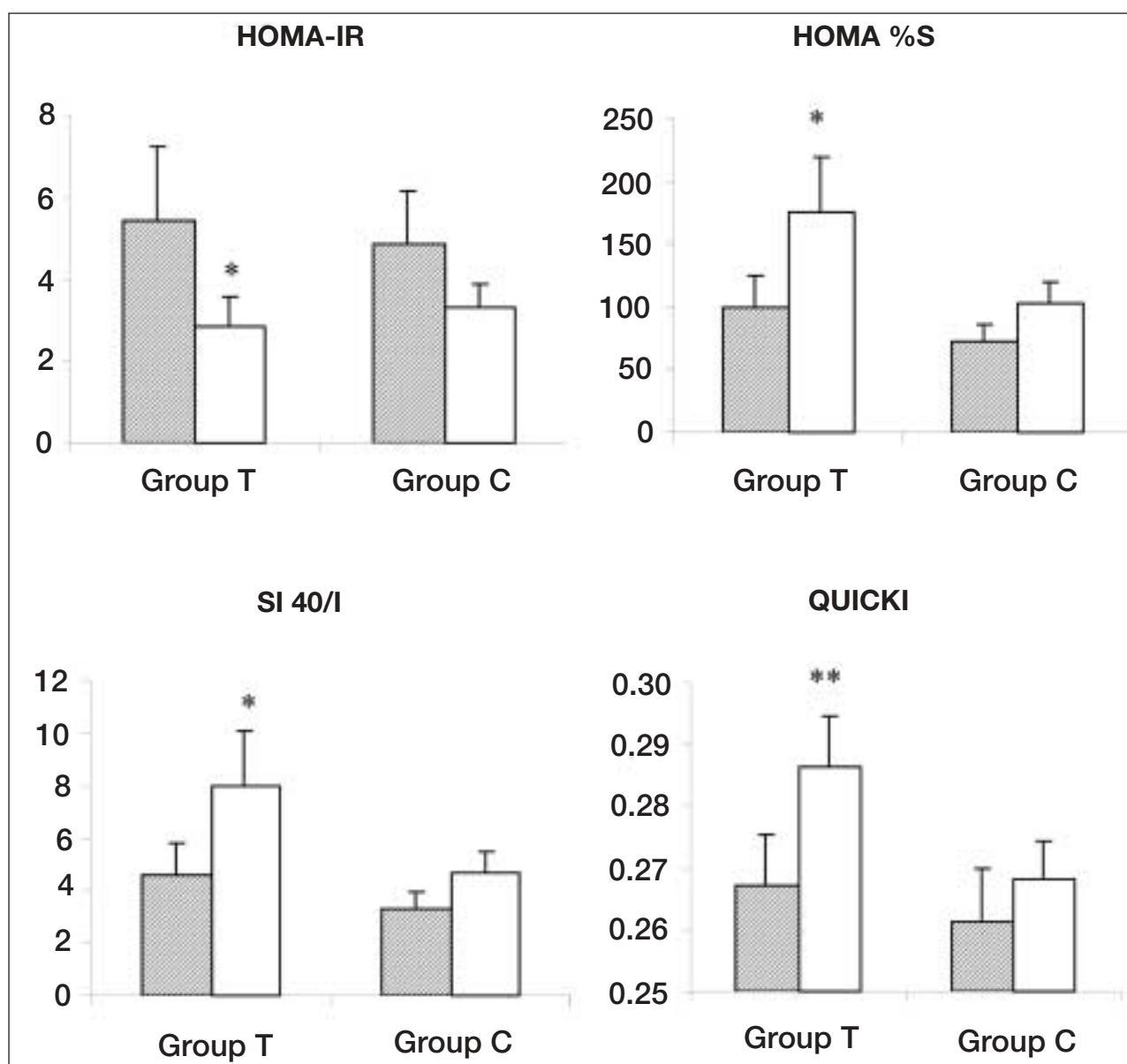
Figure 2

Surrogates measurements of insulin resistance before training session (hatched bars) and after training session (open bars) in trained (group T) and control groups (group C). Values are expressed as mean ± S.E.M.; * p<0.05; ** p<0.001 after vs before training.

Besides, lipid parameters, fibrinogen and PAI_1 did not significantly change during this training protocol. By contrast, some slight improvements in body composition could be evidenced. Fat mass significantly decreased, as reflected by bioimpedancemetry measurements, waist circumference and hip circumference. Furthermore, the decrease in percentage of fat was correlated with a decrease in both insulinemia and insulin resistance. Since both of these parameters are highly correlated, it is difficult to delineate their respective relationships with the change in fat mass. Although multivariate analysis selects rather insulinemia than insulin resistance, it should be reminded that insulinemia is the major predictor included in the calculation of the insulin resistance index. Therefore caution is required before concluding from these correlations that the decrease in fat mass influences more insulinemia than insulin resistance. On the whole, however, it should be pointed out that this two months protocol has quite moderate metabolic effects, e.g. on the lipid profile which is not improved, by contrast with what is observed during high intensity training in athletes [26, 27]. In our opinion, this does not indicate that such a training is not metabolically efficient, but that these two months represent only a first step towards a more intensive training which can be expected to have more obvious effects.

Actually, the choice to develop a training protocol targeted on the zone where lipids are oxidized needs also to be

discussed. It is now well known that exercise at low intensity (30-50% VO_{2max}) uses lipids as a fuel while carbohydrates become the predominant fuel at high intensity. On the other hand, training at high intensity improves CHO oxidation at exercise together with an increase in insulin sensitivity [28] while training at low intensity increases the ability to oxidize lipids at exercise [6, 29]. Our study gives a further demonstration of the latter assumption. Given the fact that our goal is to counteract insulin resistance, one could argue that a training protocol that increases both CHO oxidation and insulin sensitivity, as demonstrated for high intensity training, would be a more logic situation. However, our choice of a low intensity training targeted on lipid oxidation is based upon several lines of evidence. First, fat mass is clearly a worsening factor for insulin resistance [30, 31] and its reduction is well demonstrated to be beneficial for correcting the metabolic syndrome [32, 33]. On the other hand, such levels are very similar to those which have been chosen in the literature and have demonstrated their efficiency in preventing diabetes [2]. In addition, in such people who are markedly sedentary, it is surely more realistic to start training at low intensity than to propose very strenuous protocols which would probably induce an elevated percentage of discontinuations. Finally, in terms of exercise calorimetry, the most striking abnormality found in patients with obesity or NIDDM is a "glucodependence" [9], *i.e.*, an early predominance of CHO as the major fuel at exercise while lipid oxidation ability appears to be markedly impaired. Such a profile is likely to promote a further gain in fat mass which will take part in the worsening of the metabolic syndrome and it is thus logic to propose to correct it.

Interestingly, we observe two correlations supporting the concept that training-induced changes may improve lipid oxidation in these subjects: first, the lipid oxidation rate before training is proportional to the fat free mass. On the other hand, insulin sensitivity and the $LIPOX_{max}$ appear to exhibit a parallel increase during training. However, a greater sample of subjects will be necessary to investigate more precisely this issue.

Conclusion

In conclusion, this study shows that the ability to oxidize lipids at exercise is markedly improved in patients with the metabolic syndrome after two months of low intensity exercise training targeted at the level of maximal lipid oxidation. This improvement is associated with moderate but significant decreases in adiposity and insulin resistance. Such a protocol may thus represent the first step of metabolic training, which makes it possible to re-target a new training schedule at higher intensities after the power at which lipid oxidation is maximal has been shifted to the right. The metabolic efficiency of that second phase of the metabolic training is now under investigation in our unit.

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