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# Exercise targeted on maximal lipid oxidation has long-term weight-reducing effects but improves insulin secretion and lipid oxidation before reducing fat mass

## *L'exercice ciblé sur l'oxydation maximale des lipides détermine une perte de poids à long terme et améliore la sécrétion d'insuline et l'oxydation des lipides avant de réduire la masse grasse*

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**KEYWORDS**
Exercise training;
Lipid oxidation;
Insulin secretion;
Insulin sensitivity;
Minimal model;
Breakfast test;
Weight loss;
LIPOXmax;
FATmax

**Summary**
*Introduction and purpose.* — Exercise training at low intensity in the zone where lipid oxidation reaches a maximum (LIPOXmax training) has a slight but prolonged weight-lowering effect and improves both carbohydrate and lipid metabolism. We investigated in patients followed for long term LIPOXmax training which were the effect on body weight after 4 years and which were the early effects of 10 weeks of training on lipid oxidation during exercise and on insulin secretion and glucose disposal parameters measured with a standard meal.
*Methods.* — We thus present here the extension over 4 years of a preceding series of 28 obese subjects followed for 3 years to assess long-term weight-lowering effects of LIPOXmax training. In a subgroup of 14 patients undertaking such a training protocol, a breakfast test with minimal model analysis of insulin secretion and insulin sensitivity and an exercise calorimetry were performed before and after 10 weeks of targeted training.

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*Results.* — Over 48 months patients had lost on the average $-8.37 \pm 1.74$ kg, i.e. $-9.42 \pm 1.93\%$ of the initial weight ($P < 0.001$). Between 36 and 48 months weight loss was still in progress (on the average $-0.2$ kg/month). The subgroup of 14 patients undertaking LIPOXmax training showed after the initial period of 10 weeks the expected modifications of body composition in only half of the subjects, while exercise calorimetry showed an improvement of the ability to oxidize lipids during exercise ($P = 0.011$) and an increase in first phase insulin secretion ($P = 0.003$). The expected increase in insulin sensitivity was found only in 4 subjects and changes in insulin sensitivity were negatively correlated to changes in fat mass ($r = -0.608$, $P = 0.047$) and also negatively correlated to changes in beta-cell sensitivity (a measurement of second-phase insulin release) ($r = -0.710$, $P = 0.032$). There was also a correlation between changes in waist circumference and total prehepatic insulin release ($r = -0.763$, $P = 0.046$).
*Conclusion.* — Exercise training performed in the zone of maximal lipid oxidation has a sustained weigh-reducing effect that persists more than 4 years. This study demonstrates also for the first time that there are early effects on metabolism that become significant even before any obvious change in body composition. Insulin sensitivity improves when fat mass decreases and is in turn correlated with a decrease in second phase insulin secretion. By contrast the ability to oxidize lipids during exercise improves earlier, as well as phase 1 insulin secretion. Therefore, LIPOXmax training rapidly improves lipid oxidation and first phase insulin secretion, and has long lasting weight-lowering effects that further improves insulin sensitivity and reverses the insulin resistance-related excess in insulin secretion. The latter effects are not fully obtained after 11 weeks.

**MOTS CLÉS**
Entraînement en endurance ;
Oxydation lipidique ;
Sécrétion d'insuline ;
Sensibilité à l'insuline ;
Modèle minimal ;
Test du petit-déjeuner ;
Perte de poids ;
LIPOXmax ;
FATmax

**Résumé**
*Introduction et objectif.* — L'entraînement physique à faible intensité dans la zone où l'oxydation lipidique atteint un maximum (entraînement au LIPOXmax) réduit progressivement le poids corporel et améliore à la fois le métabolisme des glucides et des lipides. Nous avons étudié chez des patients suivis pour un entraînement LIPOXmax à long terme quels étaient ses effets sur le poids corporel après 4 ans et quels étaient les premiers effets de 10 semaines d'entraînement sur l'oxydation des lipides à l'exercice et sur les paramètres de sécrétion d'insuline et d'assimilation du glucose mesurés lors d'un repas-test standardisé.
*Méthodes.* — Nous présentons donc ici l'extension sur 4 ans d'une série de 28 sujets obèses précédemment suivis sur 3 ans pour évaluer les effets à long terme sur le poids corporel de l'entraînement au LIPOXmax. Dans un sous-groupe de 14 patients participant à un tel protocole de formation, un test de petit-déjeuner avec une analyse par le minimal model de la sécrétion d'insuline et de la sensibilité à l'insuline ainsi qu'une calorimétrie à l'effort ont été réalisés avant et après 10 semaines d'entraînement ciblé.
*Résultats.* — Sur 48 mois, les patients avaient perdu en moyenne $-8{,}37 \pm 1{,}74$ kg, soit $-9{,}42 \pm 1{,}93$ % du poids initial ($p < 0{,}001$). Entre 36 et 48 mois, la perte de poids était toujours en cours (en moyenne $-0{,}2$ kg/mois). Le sous-groupe de 14 patients suivant un entraînement au LIPOXmax présentait après 10 semaines les modifications attendues de la composition corporelle chez seulement la moitié des sujets, tandis que la calorimétrie à l'effort montrait une amélioration de la capacité à oxyder les lipides pendant l'exercice ($p = 0{,}011$) et une augmentation de la phase 1 de la sécrétion d'insuline ($p = 0{,}003$). L'augmentation attendue de la sensibilité à l'insuline n'a été trouvée que chez 4 sujets et ces modifications de la sensibilité à l'insuline étaient négativement corrélées aux changements de masse grasse ($r = -0{,}608$, $p = 0{,}047$) et également négativement corrélées aux changements de sensibilité au glucose des cellules bêta (qui quantifie la seconde phase de la sécrétion d'insuline) ($r = -0{,}710$, $p = 0{,}032$). Il y avait également une corrélation entre les modifications du tour de taille et la sécrétion préhépatique totale d'insuline ($r = -0{,}763$, $p = 0{,}046$).
*Conclusion.* — L'entraînement physique effectué dans la zone d'oxydation lipidique maximale détermine une perte de poids prolongée sur plus de 4 ans. Cette étude démontre également pour la première fois qu'il a des effets précoces sur le métabolisme qui deviennent significatifs avant même tout changement décelable de la composition corporelle. La sensibilité à l'insuline s'améliore lorsque la masse grasse diminue et elle-même corrélée à une diminution de la deuxième phase de sécrétion d'insuline. En revanche, la capacité à oxyder les lipides à l'exercice s'améliore plus précocement, de même que la phase 1 de la sécrétion d'insuline. Ainsi, l'entraînement au LIPOXmax améliore rapidement l'oxydation des lipides et la première phase de la sécrétion d'insuline, puis entraîne sur la durée une perte de poids qui va améliorer la sensibilité à l'insuline et corriger de ce fait l'excès d'insulinosécrétion associé à la résistance à l'insuline. Ces derniers effets ne sont pas totalement obtenus après 11 semaines.
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## 1. Introduction

There is no doubt that exercise is a cornerstone in the management of obesity [1]. However, several rather different exercise strategies are proposed [2], whose effects on metabolism and body composition are not the same [3]. Obviously, as assumed since decades [4], high volumes of exercise training have powerful effects at low intensity and even more at high intensity [5]. Among the strategies that are proposed, endurance training targeted at low intensity at the level of maximal lipid oxidation has been shown to decrease fat mass on the long term [6]. This strategy has clear beneficial effects on carbohydrate metabolism, since it induces even at low volume (170 min/week) an increase in insulin sensitivity measured with the minimal model similar to that induced by high-volume/high-intensity training and higher than that induced by low-volume/high-intensity training [7]. This is clearly a demonstration that low to moderate intensity endurance training effects on metabolism are not only due to exercise-induced energy deficit [8], but to a host of metabolic adaptations [9]. An improvement of the ability to oxidize lipids during exercise has been repeatedly described after 3 months [10,11] and after 8 months [12] of endurance training. Interestingly, pancreatic beta-cell function is also improved by low-intensity exercise training [13]. However, the report of this improvement is based on a measurement of first phase insulin response during the intravenous glucose-tolerance test and does not provide information about the second phase of insulin secretion. Recently, models aiming at evaluating the various phases of insulin secretion during an oral glucose-tolerance test or even more physiologically a standardized breakfast have provided robust assessments of these parameters available in clinical studies with a minimally invasive test [14,15]. What is known about the time course of the effects of low intensity endurance training is that it rapidly improves eating behavior [16—18] and exerts after several months a prolonged effect on body composition [6,19] and fuel metabolism [10—12,20]. Little is known on the early effects of this strategy on carbohydrate disposal and lipid oxidation, within the initial period of 10 weeks. Therefore, in this study, we investigated in a subgroup of our cohort of patients followed for long-term training performed in the zone of maximal lipid oxidation [6,19] which were the effect on the initial 10 weeks of training on exercise-induced fat oxidation, and on insulin secretion and glucose disposal parameters measured during a standard meal.

## 2. Materiel and methods

### 2.1. Patients

Patients included in this study belong to the LIPOXmax cohort, which is a database of patients followed on the long term for exercise training targeted at the level of maximal lipid oxidation (LIPOXmax training). The overall series of trained patient (new patients are still being included at this time) comprises 344 subjects, 288 women and 66 men (age 20—85 years, mean body mass index [BMI] 34.6 ± 0.36). Two comparison groups followed over 3 years have been previously presented in a previous paper [6]: a group treated by low-fat diet without exercise (34 subjects, mean age: 48.00 ± 2.41 years, mean weight: 93.48 ± 4.48 kg, mean height: 1.63 ± 0.02 m, mean BMI: 35.01 ± 1.44 kg/m$^2$) and a control group with no diet and no exercise ($n$ = 5, mean age: 38.29 ± 4.07 years, mean weight: 102.90 ± 11.05 kg, mean height: 1.68 ± 0.05; mean BMI: 35.74 ± 2.50 kg/m$^2$). Their results are shown for comparison.

The follow-up of this series of patients was continued after this period of 3 years, but data of the comparison groups are not available after 3 years. We present on Fig. 1 the follow-up of trained patients over 4 years. Patients followed over this period are 28 (Table 1).

Another subgroup of 14 patients recently included in this cohort was used for the study on the early effects of LIPOXmax training on lipid oxidation and carbohydrate homeostasis.

### 2.2. Bioelectrical impedance measurements

Prior to the exercise test, subjects' body composition was assessed with bioimpedance analysis with a six terminal impedance plethismograph BIACORPUS RX 4000 (MEDICAL HealthCare GmbH, An der Raumfabrik 31A, 76227 Karlsruhe, Germany) with data analysis with the software BodyComp 8.4. This device measures total resistance of the body to an alternative electric current of 50 kHz [21,22]. Body fat mass, fat-free mass were calculated in each segment of the body according to manufacturer's database-derived disclosed equations. Muscle mass was assessed from hand-to foot resistance at 50 kHz with Jansen's equation [23].

### 2.3. Exercise calorimetry [24—26]

Exercise calorimetry was performed after an overnight fast (12 hours) and consisted of five 6-minute steady-state workloads. Workloads were theoretically set at 20, 30, 40, 50, and 60% of Pmax, but these intensity levels can be modified during the test according to the evolution of the respiratory exchange ratio (RER = $VCO_2/VO_2$) in order to obtain values of RER below and above 0.9 which is the level of the Crossover Point (COP). Study subjects exercised on an electromagnetically braked cycle ergometer (Ergoline Bosch 500) with continuous monitoring of heart rate and electrocardiographic parameters, while metabolic and ventilatory responses were assessed with a breath-to-breath analyzing system (COSMED Quark CPET). Lipid oxidation (Lipox) and glucose oxidation (Glucox) rates were calculated by indirect calorimetry from gas exchange measurements as previously reported [20]. The balance between carbohydrates and lipids during exercise was calculated from these Lipox and Glucox values, and quantified with the maximal lipid oxidation point (LIPOXmax) and the COP. The LIPOXmax was defined as the exercise intensity at which lipid oxidation reaches its maximal level before decreasing while carbohydrate utilization further increases. It is calculated as previously reported after smoothing of the curve plotting lipid oxidation as a function of power.

The relationship between lipid oxidation and exercise intensity is expressed in two ways: gross power in watts, and percentage of $VO_2$max ACSM, i.e. aerobic fitness estimated by extrapolation of the sub-maximal levels to theoretical

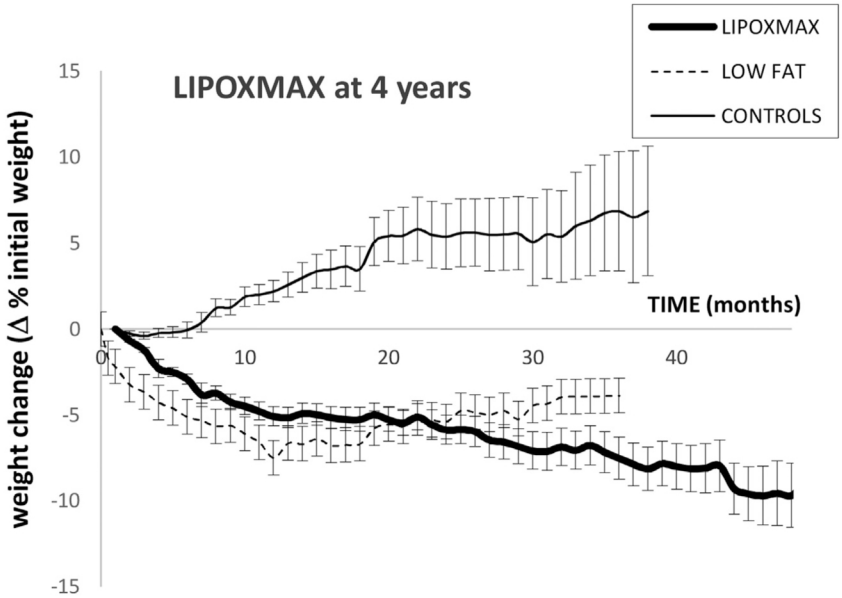


**Figure 1** Follow-up over 4 years of patients trained at the level of maximal lipid oxidation. Evolution of the percentage of initial weight of two other groups from a preceding study [6] are shown for comparison.

**Table 1** Characteristics of the 5 samples of subjects presented in this study (mean ± SEM).

| | Gender (F/M) | Age (year) | Weight (kg) | Height (cm) | BMI (kg/m$^2$) |
|---|---|---|---|---|---|
| Controls ($n$ = 5) | 4F/1M | 38.29 ± 4.07** | 102.90 ± 11.05 | 168.0 ± 5.2 | 35.74 ± 2.50 |
| Overall LIPOXmax trained cohort ($n$ = 344) | 261F/83M | 49.75 ± 0.77 | 94,04 ± 1.05 | 164.86 ± 0.47 | 34.63 ± 0.36 |
| Low-fat ($n$ = 34) | 21F/7M | 48.00 ± 2.41 | 93.48 ± 4.48 | 163 ± 2.1 | 35.01 ± 1.44 |
| Trained subjects followed over 4 years | 20F/8M | 48.31 ± 2.92 | 90.20 ± 3.43 | 164.23 ± 2.10 | 33.58 ± 1.04 |
| Subset of trained subjects investigated over the initial 10 weeks ($n$ = 14) | 10F/4M | 50 ± 2.89 | 88.16 ± 3.51 | 166.85 ± 1.68 | 31.86 ± 0.77 |

HRmax [25]. This last mode of expression is proposed by the team of P. Duché [26].

## 2.4. Breakfast test

In a subgroup of 14 individuals of the study, a standardized breakfast test was employed. This test is performed after subjects had fasted for 12 h. The meal was composed of bread (80 g), butter (10 g), jam (20 g), skimmed concentrated milk (80 ml) (Gloria SA, Paris, France), sugar (10 g), and powder coffee (2.5 g). It thus comprised 2,070 kilojoules with 9.1% proteins, 27.5% lipids, and 63.4% carbohydrates. The average time for consuming the meal was 6 min. Blood samples were taken twice before the meal and at 15, 30, 60, 90, 120, 150, 180, 210, 240 min following the start of the meal. This test, which has been designed to detect postprandial reactive hypoglycemia [27], elicits the same glycemic response as the conventional OGTT [27].

All samples were analyzed for plasma insulin by ECLIA immunoassay with a Cobas 8000 automate (Roche Diagnostics, France); the same automate was used for routine plasma glucose. Leptin was measured with the Human Leptin ELISA kit from Biovender on a Biorad Evolis device.

Insulin sensitivity was calculated with Caumo's ''oral minimal model'' [28] which is the application to OGTT or meal tests of the equations previously developed by R.N. Bergman for IVGTT [29]. It is based on the analysis of changes in plasma glucose and insulin concentration measured after the standardized breakfast. SI is given by the ''oral minimal model'' which is actually Bergman's one with simply another term called $Ra_{OGTT}$ added to the first equation. Model equations are thus:

$$\begin{cases} \dot{G}(t) = -[S_G + X(t)] \cdot G(t) + S_G \cdot G_b + \dfrac{Ra_{OGTT}(\alpha, t)}{V} & G(0) = G_b \\ \dot{X}(t) = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] & X(0) = 0 \end{cases}$$

Where G is plasma glucose concentration, I is plasma insulin concentration, suffix ''b'' denotes basal values, X is insulin action on glucose production and disposal, V is distribution volume, and $S_G$, $p_2$, and $p_3$ are model parameters. Specially, $S_G$ is the fractional (i.e., per unit distribution volume) glucose effectiveness, which measures glucose ability

per se to promote glucose disposal and inhibit glucose production; $p_2$ is the rate constant describing the dynamics of insulin action; $p_3$ is the parameter governing the magnitude of insulin action. Interestingly, these two equations can be simplified, allowing to calculate $S_I$ with a quite simple area under the curve (AUC) formula:

$$S_{I(OGTT)} = \frac{f \cdot D_{OGTT} \cdot \frac{AUC[\Delta G(t)/G(t)]}{AUC[\Delta G(t)]} - GE \cdot AUC\left[\Delta G(t)/G(t)\right]}{AUC\left[\Delta I(t)\right]}$$

Where G is plasma glucose concentration, $\Delta G$ and $\Delta I$ are glucose and insulin concentrations above basal, respectively, AUC denotes the area under the curve; GE is glucose effectiveness termed above $p_1$ or $S_G$ (dL/kg/min); $D_{OGTT}$ is the dose of ingested glucose per unit of body weight (mg/kg); and $f$ is the fraction of ingested glucose that actually appears in the systemic circulation. When glucose falls below basal, a slightly different formula needs to be used (we refer to Eq.7 in Caumo et al. [28]). Calculation of $S_I$ requires insertion of values for $S_G$ and $f$. Here we used the value of glucose effectiveness given by our previously validated formula (see below) $S_G = 2.921\ e^{-0.185(G_{60} - G_0)}$. Besides, as in Caumo's paper, the value for $f$ is set as $f = 0.8$. This ''oral minimal model'' has been validated against glucose clamp [30], sophisticated tracer experiments [31] and the classical IVGTT-based minimal model [32]. More recently we also reported its accuracy in type-2 diabetics [33].

## 2.5. Calculation of insulin secretion with C-peptide model

Insulin secretion was also quantified from C-peptide kinetics as described by the well-known two-compartment model originally proposed by Eaton et al. [34] and further improved by van Cauter et al. [35] so that the model parameters were individually adjusted to the subject's anthropometric data.

$$\dot{CP}_1(t) = -\left[k_{01} + k_{21}\right] CP_1(t) + k_{12} CP_2(t) + SR(t) \quad CP_1(0) = 0$$

$$\dot{CP}_2(t) = k_{21} CP_1(t) - k_{12} CP_2(t) \quad CP_2(0) = 0$$

Where the overdot indicates time derivative; $CP_1$ and $CP_2$ (nmol/L) are C-peptide concentrations above basal in the accessible and peripheral compartments, respectively; $k_{ij}$ ($min^{-1}$) are C-peptide kinetic parameters, and insulin secretion rate ($SR$) (pmol/L/min) is pancreatic secretion rate above basal, entering the accessible compartment, and normalized by the volume of distribution of compartment 1.

This β-cell response obtained with this classical calculation was then quantified with several classical parameters defined by the two most widely accepted models available in the literature [14,15].

The most simplistic expression was maximal insulin secretion (pMol/min/$m^2$), i.e. the highest value of ISR during the test, and total insulin release over 210 min (pMol/$m^2$) which is calculated as the area under the curve. Another measurement of total insulin secretion global index of β-cell sensitivity to glucose, $\Phi$ ($10^9$ $min^{-1}$), was calculated as follows, according to Breda [15] as the ratio between the AUC of total insulin secretion and the AUC of blood glucose concentration:

$$\Phi = \frac{\int_0^T (SR(t) + SR_b)\, dt}{\int_0^T (G(t))\, dt}$$

Where $T$ (min), the time at which the system returns to steady-state conditions after the perturbation, is in this study the duration of the glucose-tolerance test covered by blood sampling.

β-cell sensitivity to glucose [14] which is approximately equivalent to the static sensitivity index $\Phi_s$ ($10^9$ $min^{-1}$) [15] measures the effect of glucose on β-cell secretion at steady state. It is calculated as the slope (pMol/min/mmol/$m^2$) of the relationship between SR and glucose concentration.

In a recent study we reported that these two indexes of second-phase insulin response (Breda's $\Phi$ and Mari's β-cell sensitivity to glucose) are closely related to the magnitude of functional pancreatic islets mass [36,37].

Two indexes of first phase insulin secretion were measured. The derivative component, also called ''rate sensitivity'' or $k_1$ (pMol/$m^2$/mmol) according to Mari [14] is the dynamic dependence of insulin secretion on the rate of change of glucose concentration. The dynamic sensitivity index $\Phi_d$ ($10^9$) is a measure of the stimulatory effect of the rate at which glucose increases upon the secretion of stored insulin. It is defined as the amount of insulin (per unit of C-peptide distribution volume) released in response to the maximum glucose concentration ($G_{max}$) achieved during the experiment, normalized by the glucose increase $G_{max} - G_b$. This parameter $\Phi_D$ is calculated according to Breda [15].

$$\Phi_d = \frac{\int_{G_b}^{G_{max}} k(G)\, dG}{G_{max} - G_b}$$

Basal insulin secretion (pMol/min/$m^2$) given by the C-peptide kinetics was also calculated, and also expressed as an index of basal β-cell sensitivity $\Phi_b$ ($10^9$ $min^{-1}$) as follows:

$$\Phi_b = \frac{SR_b}{G_b} = \frac{k_{01} CP_{1b}}{G_b}$$

The potentiation factor ratio was also calculated according to Mari [14] as a time-varying factor, which is set to be a positive function of time and to average one during the experiment, encompassing all factors that may modulate insulin secretion (glucose and non-glucose substrates, gastrointestinal hormones, neuromodulation). It expresses a relative potentiation of the secretory response to glucose.

A disposition index was also calculated insulin secretion by insulin sensitivity, in analogy with Bergman et al. [38]. Actually, three different disposition indexes can be calculated after mixed-meal ingestion, by multiplying $k_1$, β-cell sensitivity to glucose, and total insulin secretion $\Phi$ by SI.

## 2.6. Coaching and follow-up of patients

Each subject included in the exercise group was enrolled in eight exercise sessions of 45 min at the LIPOXmax

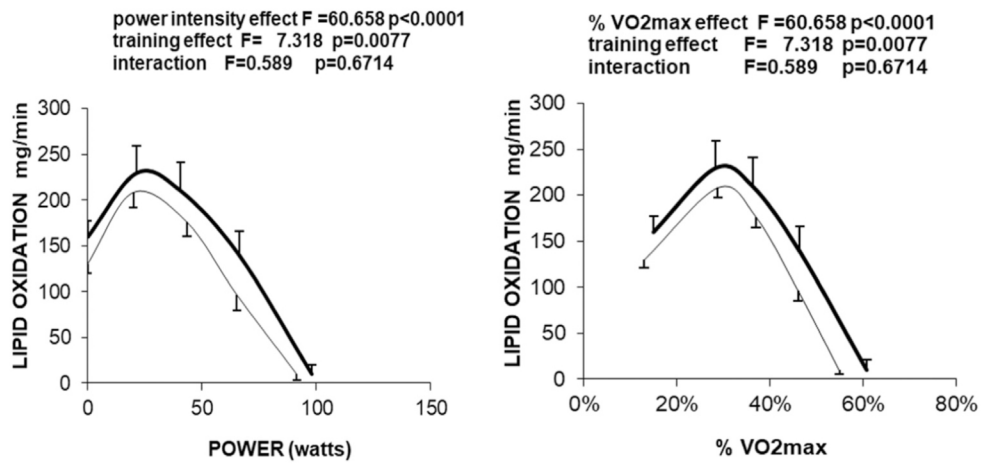


**Figure 2** Comparison of lipid oxidation curves as a function of exercise intensity (right: % $VO_2$max; left: power) before (thin line) and after (thick line) 10 weeks of training.

**Table 2** Comparison of body composition variables (weight, fat mass, lean mass and muscle mass in kg) before and after 10 weeks of targeted training at LIPOXmax (mean values ± SEM).

| | Fat mass (kg) | Fat-free mass (kg) | Muscle mass (kg) | Weight (kg) |
|---|---|---|---|---|
| Before | 34.72 ± 2.16 | 54.64 ± 2.55 | 24.7 ± 1.64 | 89.72 ± 3.81 |
| After | 33.89 ± 2.16 | 55.15 ± 2.70 | 25.49 ± 2.10 | 88.16 ± 3.51 |
| Comparison | NS | NS | NS | NS |

determined with the exercise test in order to include in his/her everyday life at least 3 similar bouts of low intensity endurance exercise per week. Subjects were followed monthly in outpatient unit for the first year and then every 3 or 4 months [39].

## 2.7. Statistics

Results are expressed as means ± standard error on the mean (SEM). The statistical analysis was performed with the Sigmastat package (Jandel Scientific, Erkrath, Germany). In this paper we used for comparisons two-way analysis of variance (ANOVA). Correlations were calculated on Microsoft Excel. Differences were considered significant at $P < 0.05$.

# 3. Results

## 3.1. Follow-up of long-term training

Our preceding training study over 36 months [6] was extended to one more year. Results on 28 patients are available (see section Methods). As shown on Fig. 2, over 48 months these patients had lost on the average −8.37 ± 1.74 kg, i.e. −9.42 ± 1.93% of the initial weight ($P < 0.001$). Between 36 and 48 months weight loss still continued at a low rate (on the average −0.2 kg/month). The follow-up of the groups ''low-fat diet only'' and ''control' were stopped after 36 months but if compared to the results of regular training weight loss was lower (−3.88 ± 2.26% in the former and +6.86 ± 3.75 in the latter, $P < 0.001$ for both compared to the training group). Clearly low-fat diet without training was no longer efficient and was followed by weight regain, and the lack of any management of obesity was associated with a gradual weight gain.

## 3.2. Subgroup of 14 patients followed over 10 weeks

The follow-up was maintained in the outpatient unit over 10 weeks, and patients on the average performed 2 sessions in the unit and one or more at home.

### 3.2.1. Body composition

As shown on Table 2, after 10 weeks of training the expected changes in body composition are observed only in half of the subjects and thus do not reach significance. Six subjects lost weight with a weight loss ranging from 0.5 to 3.9 kg. On the whole sample weight loss (−0.16 ± 0.74 kg) does not reach significance. Six subjects lost between 1.4 to 6.9 kg of fat mass. Similarly at this stage fat mass loss was not yet found to be significant (−0.88 ± 1.32 kg). Lean body mass only increased in 3 subjects ranging from 1.2 to 6.7 kg. No significant change in lean mass was evidenced −0.009 ± 0.81 kg. Muscle mass assessed by Jansen's equation is also practically unchanged +0.027 ± 0.94 kg (non-significant values).

### 3.2.2. Eating behavior

After 10 weeks of LIPOXmax training we do not observe any significant change in daily food ingestion despite a non-significant tendency to decrease caloric intake, consumption of lipids and carbohydrates and to increase consumption of proteins (Table 3). By contrast if we look at individual

**Table 3** Comparison of average calorie intake values (Kcal/24 h) and percentage of daily carbohydrates, lipids and proteins before and after 10 weeks of targeted training at LIPOXmax (average values + SEM).

| | Total calorie intake (Kcal/24 h) | Protein intake (%) | Lipid intake (%) | CHO intake (%) |
|---|---|---|---|---|
| Before | 1983.2 ± 183.2 | 18.4 ± 2.4 | 30.0 ± 3.7 | 51.9 ± 4.5 |
| After | 1972.4 ± 165.5 | 20.3 ± 2.4 | 28.3 ± 2.8 | 51.4 ± 3.5 |
| Comparison | −38.6 ± 171.9 | 1.9 ± 2.0 | −1.7 ± 2.3 | −0.4 ± 2.7 |
| | NS | NS | NS | NS |

**Table 4** Comparison of the average values of power associated with LIPOXmax (Watt), of maximum lipid oxidation rate (mg/min) and of maximum lipid oxidation rate per kilo of muscle (mg/min/kg of muscle) before and after 10 weeks of training (average values ± SEM).

| | Power associated with LIPOXmax (Watt) | Maximum lipid oxidation rate (mg/min) | Maximum lipid oxidation rate (mg/min/kg of muscle) |
|---|---|---|---|
| Before | 45.01 ± 7.16 | 219.3 ± 13.51 | 9.27 ± 0.70 |
| After | 47.14 ± 4.32 | 232.01 ± 16.63 | 10.02 ± 0.65 |
| Comparison | NS | 44.01 ± 14.19* | 2.15 ± 0.77* |
| | | $P < 0.05$ | $P < 0.05$ |

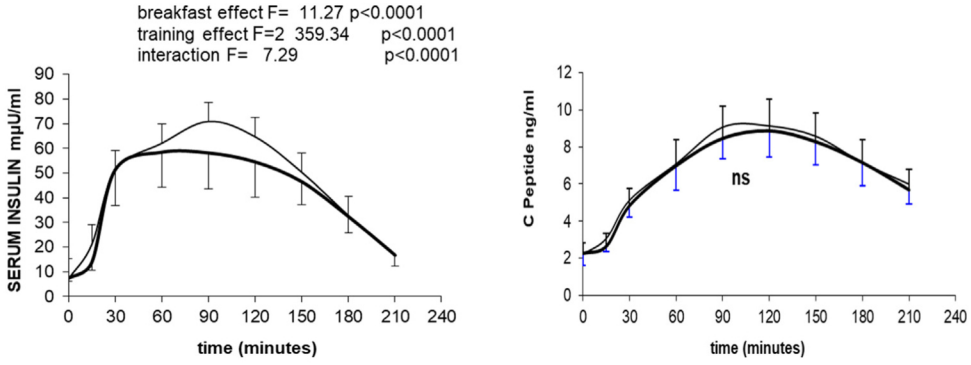


**Figure 3** Insulin and C-peptide values before (thin line) and after (thick line) 10 weeks of training. ANOVA detects a post-training decrease in insulin ($P < 0.0001$) but not in C-Peptide. At time 30 insulin value is lower after training ($P = 0.045$). For C-Peptide this effect does not reach significance ($P = 0.057$).

responses we note that 6 subjects reduced their caloric intake from 56 to 790 kCal, but this reduction was not significant on the total sample. By contrast (data not shown) there was a modification of questionnaires of appetite with a decrease in reported hunger and an increase in the feeling of satiety. This effect occurred on the first week and remained at steady state over the 10 weeks of observation. This aspect of the study will be the matter of another separate report.

### 3.2.3. Exercise calorimetry

After the 10 weeks of training, exercise calorimetry shows an increase in the ability to oxidize lipids during exercise, expressed in various ways (Table 4). There is a significant increase (+44.01 ± 14.19 mg/min; $P = 0.011$) in maximum lipid oxidation flow rate of as well as a significant increase (2.15 ± 0.77 mg/min/kg of muscle; $P = 0.021$) in lipid oxidation flow rate maximum.

### 3.2.4. Blood tests

*3.2.4.1. Leptin.* After the targeted rehabilitation at LIPOXmax there is a non-significant decrease in leptin levels tendency ranging from 28.4 ± 5.17 ng/mL at T0 versus 21.1 ± 5.38 ng/mL at T10. As well as a non-significant tendency to decrease leptinemia compared to the mass thanks ranging from 0.79 ± 0.12 ng/mL/kg at T0 versus 0.59 ± 0.10 ng/mL/kg at T10.

*3.2.4.2. Breakfast test.* After 10 weeks of LIPOXmax training, a downward trend in insulin postmeal response could be observed (Fig. 3). The increase in insulin was significantly lower ($P = 0.045$ at 30 min) but this effect was not significant for C-peptide. Fig. 4 shows prehepatic insulin secretion rates reconstructed from C-peptide kinetics. On the left panel it can be seen that the two-way ANOVA (Postmeal time × Training level) shows a significant effect on prehepatic insulin secretion values (pMol/min/m$^2$) for the time factor (F = 18.035; $P < 0.001$), and no significant effect

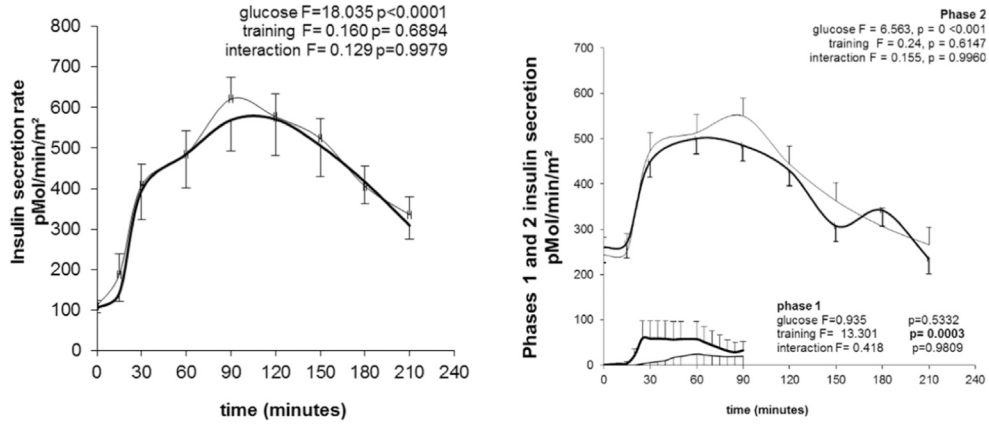


**Figure 4** Prehepatic insulin secretion rate reconstructed according to C-peptide kinetics before (thin line) and after (thick line) 10 weeks of training. Left: overall secretion (no significant effect of training at this time). Right: prehepatic insulin secretion rates analyzed in terms of first phase and second phase insulin release, showing no training effect at this time on second phase but an early improvement of phase 1.

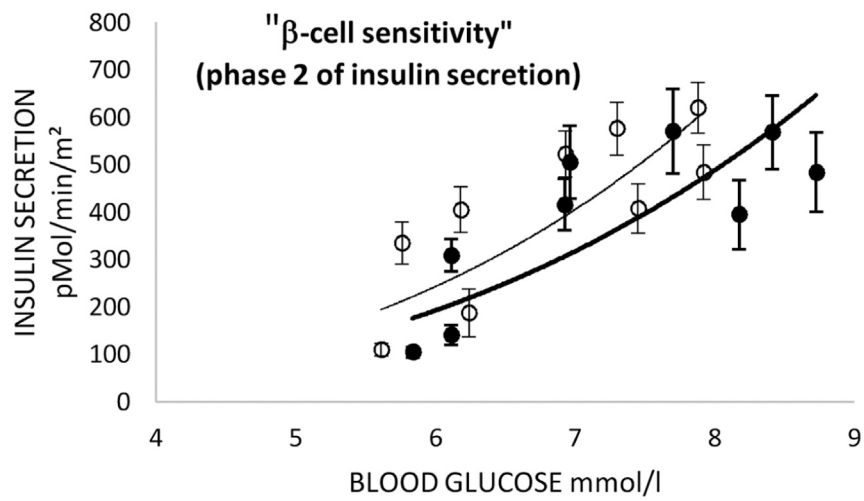


**Figure 5** ''Beta-cell sensitivity'' according to Mari's model, i.e., prehepatic insulin secretion in pMol/min/m$^2$ as a function of blood glucose level mmol/L before (thin line) and after (thick line) 10 weeks of training. It is a measurement of phase 2 of insulin secretion. No significant change at this stage.

**Table 5** Comparison of parameters of glucose disposal before and after 10 weeks of training (average values ± SEM).

| | Insulin sensitivity (min$^{-1}$/μU/mL) × 10$^{-4}$ | Insulin peripheral clearance (min$^{-1}$) | Insulin hepatic extraction (%) |
|---|---|---|---|
| Before | 5.86 ± 0.93 | 0.18 ± 0.02 | 70.83 ± 4.63 |
| After | 6.77 ± 1.65 | 0.20 ± 0.02 | 73.28 ± 4.23 |
| Comparison | NS | NS | NS |

for either training factor (F = 0.160; $P$ = 0.6894) or interaction (F = 0.129; $P$ = 0.9979). Therefore, no training effect is detected for the overall prehepatic insulin response. By contrast as can be seen on Fig. 4 (right panel), the ANOVA evidenced a significant effect on the first phase insulin secretion (pMol/min/m$^2$) for the training factor (F = 13.301; $P$ = 0.003). During phase 2 of insulin secretion, the two-factor ANOVA (Glycemia × Training level) showed a significant effect on the insulin secretion values (pMol/min/m$^2$) for postmeal time (F = 6.563; $P$ = 0 < 0.001), no significant effect for training (F = 0.24; $P$ = 0.6147) and interaction (F = 0.155; $P$ = 0.9960).

Fig. 5 shows beta-cell sensitivity (a measurement of phase 2 insulin secretion according to Mari's model) before and after 10 weeks of rehabilitation. Phase 2 insulin secretion tends to have a slower slope, but the difference is not significant.

The expected increase in insulin sensitivity is not found significantly (Table 5). Actually this parameter increases only in 4 subjects. Table 5 also shows the values of peripheral

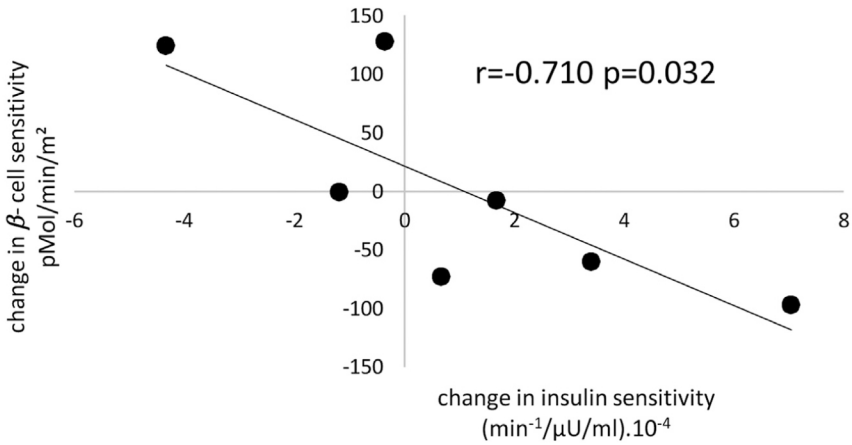


**Figure 6** Negative correlation between changes in ''Beta-cell sensitivity'' according to Mari's model, i.e., prehepatic insulin secretion in pMol/min/$m^2$ as a function of blood glucose level and changes in insulin sensitivity.

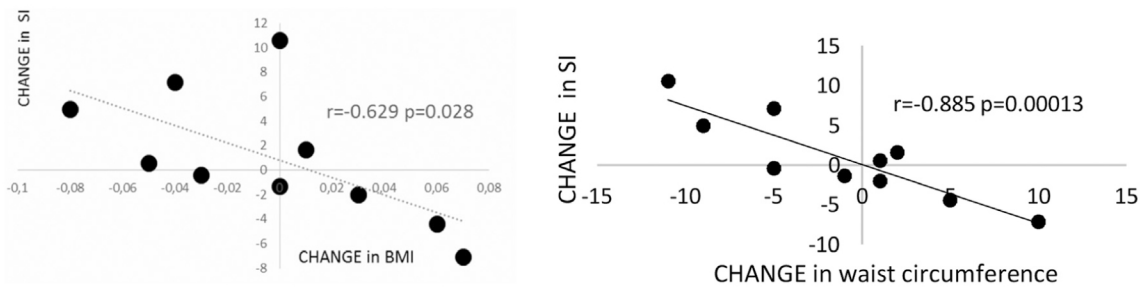


**Figure 7** Correlation between change in insulin sensitivity ($min^{-1}/\mu U/mL$) $\times 10^{-4}$ and change in BMI (left) and waist circumference (right).

insulin clearance and hepatic insulin extraction which are not significantly modified despite a tendency to increase. Fig. 6 shows that changes in beta-cell sensitivity are negatively correlated to changes in insulin sensitivity, i.e., when insulin sensitivity increases phase 2 insulin release decreases ($r = -0.710$; $P = 0.032$). Fig. 7 shows that changes in insulin sensitivity are correlated to changes in body mass index and waist circumference. Other correlations (graphs not shown) are found. There is a correlation between changes in insulin sensitivity and changes in fat mass ($r = -0.608$; $P = 0.047$). There is also a correlation between changes in waist circumference and total prehepatic insulin release ($r = -0.763$; $P = 0.046$) and between initial carbohydrate intake and weight change ($r = 0.725$; $P = 0.027$, i.e. subjects eating less CHO lose more weight).

## 4. Discussion

This study confirms that endurance training targeted at low intensity at the level of maximal lipid oxidation is able to reduce body weight over a long period (more than 4 years). It demonstrates also for the first time that there are early effects on metabolism that become significant even before any obvious change in body composition. At 10 weeks, fat loss is found in only half of the patients, and is associated with an increase in insulin sensitivity which is in turn correlated with a decrease in second phase insulin secretion. At this time however, a highly significant improvement in lipid oxidation during exercise is evidenced, as well as an improvement in phase 1 insulin secretion.

This improvement in phase 1 insulin secretion is consistent with the previous report of an increase in acute insulin response to intravenous glucose [13]. This is the first time that this effect is demonstrated with the technique of the oral minimal model.

Whether physical exercise can be a therapy for improving beta-cell function has been investigated since more than two decades [40] and is now supported by a large body of evidence [41]. Two large-scale studies confirm this effect, namely the Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE) on 179 subjects [13] and the HEalth, RIsk factors, exercise Training And Genetics (HERITAGE) involving 596 subject [42]. Both studies employed the intravenous glucose-tolerance test which yields a parameter AIRg which is a well-recognized measurement of phase 1 insulin response. Such studies and others on smaller populations [43,44] lead to the concept that the effect of exercise on insulin secretion may be even more important for improving glucose homeostasis in prediabetic subjects than the classical effect on insulin sensitivity [45]. Accordingly, attempts to preserve beta-cell function in patients with type 1 diabetes with exercise training have been performed [46].

It is interesting to notice that low-intensity endurance exercise, i.e., the kind of exercise used in the current study, has been reported to be more efficient than high-intensity exercise for improving beta-cell function

[13,44]. This effect, together with the long-term sustained weight-reducing efficacy, emphasizes the interest of this easy-to-perform variety of training in patients with obesity and metabolic syndrome.

An effect on phase 2 of insulin secretion is not evidenced in this study but we do not know if it may occur later. The correlation found between changes in SI and changes in phase 2 suggests that these two parameters will undergo simultaneous alterations when body fat stores will be more markedly decreased, resulting in a significant improvement of insulin sensitivity. In addition, in subjects of this study, phase 2 was not impaired and thus an increase in magnitude may not be expected. The logic effect could be that when insulin sensitivity increases, phase 2 decreases to avoid hypoglycemia, according to the classical homeostatic loop evidenced by the team of R.N. Bergman.

The use of mathematic modelling of a meal test requires some comments. This approach is not so widely employed due to its apparent conceptual complexity, but it has two advantages: the simplicity of its technical procedure and the powerful analysis it can provide for cell function. This approach has demonstrated good reproducibility in various metabolic profiles. In this study we calculated insulin delivery in the portal circulation ISR (t) with Van Cauter's C-peptide kinetics analysis. This calculation is unanimously considered as robust and has been said by Claudio Cobelli to be almost model-independent [47]. β-cell sensitivity to glucose, as proposed by Mari in his model [14], is also a robust parameter that expresses ISR (t) as a function of blood glucose concentration. It represents the static component of insulin secretion, also termed second-phase of insulin secretion. Recent literature has highlighted its pathophysiological relevance. It has been shown to be a major determinant of glucose tolerance [48], and to predict the evolution toward diabetes [49]. Improvement of this parameter largely explains the remission of diabetes which is observed after bariatric surgery [50,51]. A defect in this parameter results in impaired glucose tolerance [52]. Recently, it was reported that this parameter is proportional to beta-cell mass [53], a finding which is further supported by a recent study in our center [36,37].

It is however intriguing to find an effect of training on crude insulin levels while this effect is not evidenced on C-peptide levels, neither it is evidenced on the overall prehepatic insulin secretion rates. This may be due to changes in insulin clearance, but neither peripheral nor hepatic insulin removal (Table 5) are significantly modified. Actually there is a non-significant tendency to the increase of both parameters that can become significant on a higher sample and/or after a longer training period. This will be interesting to assess since insulin clearance is hypothesized to be an important factor of glucoregulation whose defect is supposed to play a role in the decline of glucose homeostasis that leads to type-2 diabetes [54,55].

The natural history of the effects of LIPOXmax training as evidenced by previous studies and by this one can thus be summarized as follows. This training applied at low volume (3 × 45 min/week) rapidly modifies eating behavior [16—18] and the ability to oxidize lipids during exercise (this study). After 10 weeks first phase insulin secretion is restored (this study). Later, there is a gradual loss in fat mass which is still going on over almost 4 years. It results in a host of improvements in lipid profile, insulin sensitivity, low-grade inflammation, that are clearly evidenced after 3 months [39]. After 2 years [19] fat-free mass is decreased, and this decrease is likely to reflect a profound reorganization of body composition. This decrease is associated with a decrease in blood pressure which is already observed at 3 months, although at this stage it is more moderate than the effect of high intensity interval training [20]. Effects on insulin clearance that are not yet evidenced but that are suggested by some non-significant tendencies in the current work need to be investigated.

## 5. Conclusion

This work therefore shows that:

- the weight loss determined by this type of training persists at least for 4 years;
- the restoration of an ability to oxidize fat during exercise is an early event which precedes the other expected effects (loss of fat mass, improvement in glucoregulation), which begin to develop at 10 weeks in only half of the subjects;
- phase 1 insulin secretion is restored very early even before the improvement of insulin sensitivity, confirming that this kind of training rapidly improves insulin secretion.

Further studies on this cohort are in progress in order to better understand the time course of the various effects of LIPOXmax training and to assess its efficacy on a longer period.

## Disclosure of interest

The authors declare that they have no competing interest.

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