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Trabajo Original

Obesidad y síndrome metabólico

# Cardiorespiratory fitness and fat oxidation during exercise as protective factors for insulin resistance in sedentary women with overweight or obesity

## *Fitness cardiorrespiratorio y oxidación de grasas durante el ejercicio como factores protectores de resistencia a la insulina en mujeres sedentarias con sobrepeso u obesidad*

Javiera Cancino-Ramírez[1-2], Johana Soto-Sánchez[3], Hermann Zbinden-Foncea[4], Manuel Moreno González[5], Bárbara Leyton-Dinamarca[6] and Luis González-Rojas[2-4]

*[1]Magíster de Fisiología Clínica del Ejercicio. Facultad de Medicina. Universidad Mayor. Santiago, Chile. [2]Centro de Tratamiento de la Obesidad. Pontificia Universidad Católica de Chile. Santiago, Chile. [3]Facultad de Ciencias de la Actividad Física del Deporte y Recreación. Departamento de Educación Física. Universidad de Playa Ancha. Valparaíso, Chile. [4]Laboratorio de Ciencias del Ejercicio. Escuela de Kinesiología. Facultad de Medicina. Universidad Finis Terrae. Santiago, Chile. [5]Departamento de Nutrición, Diabetes y Metabolismo. Facultad de Medicina. Pontificia Universidad Católica de Chile. Santiago, Chile. [6]Instituto de Nutrición y Tecnología de los Alimentos Doctor Fernando Monckeberg Barros. Universidad de Chile. Santiago, Chile*

## Abstract

**Introduction:** obesity is a global pandemic and it is the biggest risk factor for death worldwide nowadays. Studies suggest that both cardiorespiratory fitness and fat oxidation in exercise are related to insulin resistance and type 2 diabetes mellitus, and they could be used as metabolic fitness markers.

**Objectives:** the aim of this study is to determine if cardiorespiratory fitness ($VO_2$) and fat oxidation during exercise are protective factors of insulin resistance (IR) in sedentary women with obesity or overweight.

**Methods:** sixty women were selected for fat oxidation analysis and 55 for cardiorespiratory fitness analysis that fitted the inclusion and exclusion criteria. $VO_2$, maximal fat oxidation (MFO) and the intensity where MFO is reached (FATmax) were determined through an incremental test on a cycle ergometer with gas analysis. The subjects with a Homeostatic model assessment of IR index greater or equal to 2.5 were considered as insulin-resistant. Participants were divided into 2 groups, IR group (n = 38) and Non-IR group (n = 22).

**Results:** $VO_{2(\%)}$ and MFO were lower in the IR group (76.1% *vs.* 83.2%; p = 0.015 and 1.08 mg × $kg^{-1}$ × $min^{-1}$ *vs.* 1.62 mg × $kg^{-1}$ × $min^{-1}$; p = 0.044, respectively) compared to the Non-IR group. There was an association between $VO_{2(\%)}$ and IR (OR = 0.92, p = 0.017) and between MFO and IR (OR = 0.52, p = 0.035), both models adjusted for age and body mass index.

**Conclusions:** $VO_{2(\%)}$ and MFO are independent protective factors for IR. No association was found between FATmax and IR.

**Key words:**

Cardiorespiratory fitness. Lipid metabolism. Insulin resistance. Cardiopulmonary exercise test. Oxygen consumption.

## Resumen

**Introducción:** la obesidad es una pandemia global y actualmente es el mayor factor de riesgo de muerte a nivel mundial. Estudios sugieren que tanto el *fitness* cardiorrespiratorio ($VO_2$) como la oxidación de grasas durante el ejercicio podrían ser utilizados como marcadores del *fitness* metabólico.

**Objetivos:** el objetivo de este estudio es determinar si el $VO_2$ y la oxidación de grasas durante el ejercicio son factores protectores de resistencia a la insulina en mujeres sedentarias con obesidad o sobrepeso.

**Métodos:** fueron seleccionadas 60 mujeres para análisis de oxidación de grasas y 55 para análisis de $VO_2$ que cumplieran con los criterios de inclusión y exclusión. El $VO_2$, la máxima oxidación de grasas (MFO) y la intensidad donde se alcanza el MFO (FATmax) fueron determinados mediante un test incremental en cicloergómetro con análisis de gases. Los sujetos con un índice HOMA-IR mayor o igual a 2,5 fueron considerados con resistencia a la insulina. Los participantes fueron divididos en dos grupos, IR (n = 38) y No-IR (n = 22).

**Resultados:** el $VO_{2(\%)}$ y la MFO fueron menores en el grupo IR en comparación al grupo No-IR (76,1% *versus* 83,2%; p = 0,015 y 1,08 mg × $kg^{-1}$ × $min^{-1}$ *versus* 1,62 mg × $kg^{-1}$ × $min^{-1}$; p = 0,044, respectivamente). Mediante el análisis de regresión logística se encontró una asociación entre $VO_{2(\%)}$ e IR (OR = 0,92; p = 0,017) y entre MFO e IR (OR = 0,52; p = 0,035), ambos modelos ajustados por edad e índice de masa corporal.

**Conclusión:** el $VO_{2(\%)}$ y la MFO son factores protectores independientes de IR. No se encontró asociación entre el FATmax y la IR.

**Palabras clave:**

*Fitness* cardiorrespiratorio. Metabolismo de lípidos. Resistencia a la insulina. Prueba de esfuerzo cardiopulmonar. Consumo de oxígeno.

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Correspondence:

Luis González Rojas. Laboratorio de Ciencias del Ejercicio. Escuela de Kinesiología. Facultad de Medicina. Universidad Finis Terrae. Av. Pedro de Valdivia 1509, Santiago, Chile
e-mail: rojas.gonzalez.luis@gmail.com

## INTRODUCTION

Many studies suggest that a lipids oversupply in peripheral tissues could contribute to insulin resistance (IR) development (1). Subjects with IR frequently show an abnormal lipids metabolism including an increase of free fatty acids, an elevated content of intramyocellular lipids, and an impaired mitochondrial fatty acid oxidation (1-3).

On the other hand, multiples studies have related IR with mitochondrial oxidative capacity, which, in effect, is strictly related to fat oxidation and total body oxidative capacity (4). Oxygen consumption ($VO_2$) is a reflex of this oxidative capacity and many authors suggest that higher values of $VO_2$ substantially reduce the adverse effects of obesity on morbidity and mortality (5), and that lower levels of $VO_2$ predispose to metabolic conditions such as IR and type 2 diabetes mellitus (6).

Just as $VO_2$, maximal fat oxidation during exercise reflects mitochondrial respiration and, since their changes are related to mitochondrial fat oxidation capacity, it could be used as metabolic fitness markers (7,8).

Physical training is one of the non-pharmacological actions most used in the prevention and treatment of IR, and diverse studies have related physical fitness with insulin sensitivity (9). Nevertheless, there are no studies that determine the protective role of aerobic capacity and fat oxidation on IR. The aim of this study is to determine the protective role of cardiorespiratory fitness and fat oxidation during exercise on IR in sedentary women with obesity or overweight.

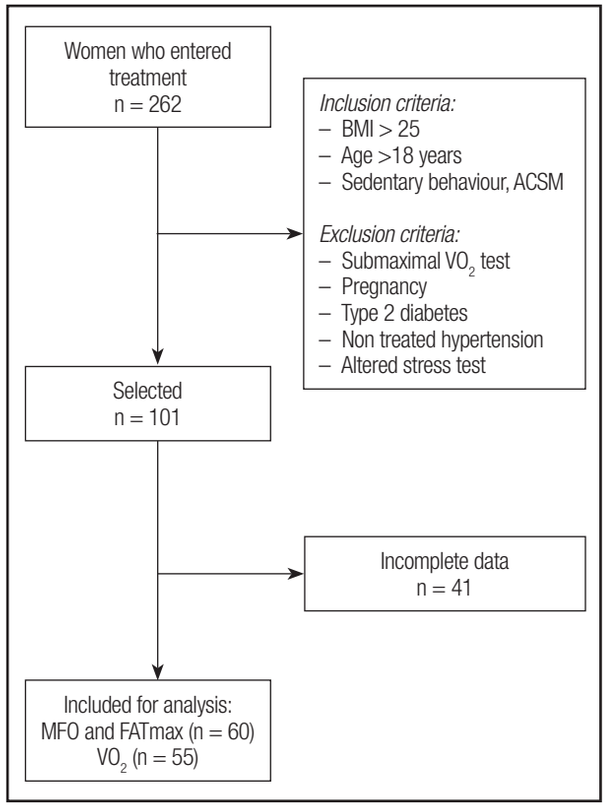


**Figure 1.**

Sample's selection flow chart (BMI: body mass index; ACSM: American College of Sports Medicine; $VO^2$: maximal oxygen consumption; MFO: maximal fat oxidation; FATmax: intensity were MFO is reached).

## MATERIALS AND METHODS

### STUDY DESIGN

This study was conducted in accordance with the Declaration of Helsinki and was approved by Ethics Committee with a waiver of the need to obtain informed consent (register 15-267). All participants' data were obtained from our retrospective database at Obesity Treatment Center according to inclusion/exclusion criteria.

### PATIENTS

We identified 60 women who met the criteria shown in Figure 1 that were selected in a non-probabilistic way.

### Body composition

Height was measured with a stadimeter (0.5 cm precision) and weight with a SECA digital scale (0.1 kg precision). Both assessments were performed without shoes and in light clothing. Body mass index (BMI) was calculated as weight × height$^{-2}$ (kg × m$^{-2}$). Lean and fat mass was assessed by octopolar multifrequency bioimpedance (10) in 4 hours fasting state, without menstruation and with at least 12 hours free of exercise.

### Cardiorespiratory fitness

An incremental cycle ergometer test was performed with gas analysis (Metalyzer 3B-R2, Cortex). The patients were free of exercise, alcohol, coffee, drugs or other stimulants consumption in the previous 24 hours and in a 6 hours fasting condition. Theoretical maximal load ($W_t$) was estimated by Jones equation in Watts (11). Protocol consisted in a 3-minutes rest period, then a 3-minutes warm up at 20% of $W_t$ followed by 6 minutes stages at 30, 40, 50 and 60% of $W_t$ until a respiratory exchange ratio (RER) ≥ 1 was reached. Then 1-minute stages were performed with increases of 10% of $W_t$ until exhaustion. Verbal stimuli were allowed. The test was considered as maximal if a RER ≥ 1.1 was reached and/or if the maximal heart rate ($HR_{max}$) was greater or equal to the theoretical maximum predicted by Morris equation for ergometer cycle test (12). This protocol was adapted from the one proposed by Brun, Romain and Mercier (7). The next variables were calculated from the average of the final 30 seconds from the last completed stage (breath by breath): $HR_{max}$ in beats x min$^{-1}$, maximal load

in Watts ($W_{max}$), maximal load expressed as a percentage of $W_t$ ($W_{max(\%)}$) and relative to body weight in watts x kg ($W_{max\ rel}$).

The same methodology was used for determining cardiorespiratory fitness from the measurements of maximal oxygen consumption. This was expressed as an absolute value in L × $min^{-1}$ ($VO_{2max}$) and as a percentage of the maximum estimated ($VO_{2max(\%)}$) according to the Wasserman and Hansen weight algorithm (13).

### Fat oxidation

Frayn equations were used (14) with the average value of oxygen and carbon dioxide volumes of the last 2 minutes of every completed stage of 6 minutes. Was calculated: a) maximal fat oxidation rate (MFO), that is the maximum fat amount used during an incremental workload exercise and is expressed as an absolute value (g × $hour^{-1}$) and relative to body weight and to fat free mass (mg × $kg^{-1}$ × $min^{-1}$); and b) the intensity or workload where MFO is reached (FATmax), expressed as percentage of $W_t$ (FATmaxW) and as a percentage of theoretical maximum oxygen consumption ($FATmaxVO_2$) (13).

### Insulin resistance

The homeostatic model assessment of insulin resistance (HOMA-IR) proposed by Mathews et al. (15) was used. Patients were considered with insulin resistance if they had a HOMA-IR value greater or equal to 2.5 according to the existent literature (16).

## STATISTICAL ANALYSIS

The sample was categorized into two groups according to the presence of IR. Distribution of the variables was assessed with Kolmogorov-Smirnov test. Variables with normal distribution are presented as mean and standard deviation and those without normal distribution are shown as a median and in the 25-75 percentile. For comparing means between both groups a Student's t-test for independent samples was used for variables with normal distribution and a Wilcoxon test for non-normally distributed variables. For association of IR with cardiorespiratory fitness and exercise fat oxidation a stepwise logistic regression analysis was performed, adjusting by age and BMI. Data are presented as *odds ratio* and confidence interval of 95%. The goodness of fit was evaluated with a Hosmer-Lemeshow test.

For all the analysis a p-value < 0.05 was considered significant. A sample size analysis revealed that a 42 subjects sample is enough to obtain statistical power with a power of 0.8 and an alpha of 0.05 (17). Statistical analysis was performed with the computational statistics program STATA 12 (Stata Corp, College Station, TX).

## RESULTS

General characteristics of the subjects are shown in table I. IR group presents a higher weight, BMI, fat mass and body fat percent in contrast to Non-IR group, whereas this last one presents a greater amount of fat-free mass.

Table II shows the differences in cardiorespiratory fitness and fat oxidation between both groups. $VO_{2max(\%)}$ and MFO were lower in the IR group in a 7.1% and 33.3%, respectively.

Table III shows logistic regression models for the association of IR with $VO_{2max(\%)}$, MFO and FATmax, adjusted by age and BMI. Models a) and b) were statistically significant and both are valid according to the Hosmer-Lemeshow goodness of fit test (p = 0.056 and p = 0.309, respectively).

**Table I.** General characteristics

| | No-IR (n = 22) | IR (n = 38) | p-value |
|---|---|---|---|
| Age[1] (years) | 35.4 ± 10.2 | 30.6 ± 8.5 | 0.028* |
| Weight[2] (kg) | 74.7 (69.6-81.0) | 81.8 (79.1-88.8) | 0.007† |
| Height[1] (cm) | 161.9 ± 8.1 | 159.3 ± 5.7 | 0.054 |
| BMI[2] (kg × $m^{-2}$) | 29.4 (28.1-31.8) | 32.8 (30.6-35.9) | 0.001† |
| FFM[1] (kg) | 42.2 ± 5.8 | 42.4 ± 4.9 | 0.445 |
| FFM[2] (%) | 53.2 (51.5-57.1) | 50.1 (46.9-53.1) | 0.006† |
| FM[2] (kg) | 33.6 (26.6-41.3) | 38.8 (35.1-42.8) | 0.016† |
| FM[1] (%) | 43.3 ± 8.4 | 46.8 ± 4.8 | 0.023* |
| Fasting glycemia (mg × $dL^{-1}$) | 84.8 ± 5.3 | 89.3 ± 8.0 | 0.022* |
| Fasting insulinemia (mg × $dL^{-1}$) | 10.1 (8.7-11.8) | 19.3 (15.4-28.9) | 0.000† |
| HOMA-IR | 2.1 (2.0-2.5) | 4.2 (3.4- 5.8) | 0.000† |

*BMI: body mass index; FFM: fat free mass; FM: fat mass; HOMA-IR: homeostatic model assessment.*
*[1] Values are expressed as mean (±) standard deviation; [2]Values are expressed as median (p25-75).*
**Student's t test for independent samples: p < 0.05. †Wilcoxon test for independent samples: p < 0.05.*

**Table II.** Cardiorespiratory fitness and fat oxidation

| | No-IR (n = 22) | IR (n = 38) | p-value |
|---|---|---|---|
| $VO_{2max}$ (L × min$^{-1}$) | 1.53 ± 0.27[b] | 1.51 ± 0.28[c] | 0.386 |
| $VO_{2maxrel}$ (mL × kg-1 × min$^{-1}$) | 24.3 ± 3.1[b] | 23.9 ± 3.2[c] | 0.321 |
| $VO_{2max}$ (%) | 83.2 ± 10.2[b] | 76.1 ± 11.9[c] | 0.015* |
| Maximal load ($W_{max}$) | 108.3 ± 27.0[b] | 110.8 ± 24.1[c] | 0.360 |
| Maximal load ($W_{max(\%)}$) | 88.1 ± 24.8[b] | 88.6 ± 17.7[c] | 0.460 |
| MFO (g × h$^{-1}$) | 7.63 ± 6.6 | 5.4 ± 5.0 | 0.076 |
| MFO (mg × kg$^{-1}$ × min$^{-1}$) | 1.62 ± 1.37 | 1.08 ±1.01 | 0.044* |
| MFO[a] (mg × kg$^{-1}$ × min$^{-1}$) | 3.0 ± 2.6 | 2.2 ± 2.0 | 0.073 |
| FATmax W (%) | 33.4 ± 5.7 | 32.1 ± 5.5 | 0.198 |
| FATmax $VO_2$ (%) | 46.1 ± 9.0 | 45.3 ± 8.5 | 0.358 |

*$VO_{2max}$: maximal oxygen consumption; MFO: maximal fat oxidation rate.*
*Values are expressed as mean (±) standard deviation.*
*[a]kg of fat free mass; bn = 20; cn = 35. *Student's t test for independent samples: p < 0.05*

**Table III.** Logistic regression for association of IR with $VO_{2max}$ and fat oxidation

| Model** | OR | 95% CI | p-value |
|---|---|---|---|
| a) $VO_{2max(\%)}$ | 0.92 | 0.87-0.97 | 0.017* |
| b) MFO (mg × kg$^{-1}$ × min$^{-1}$) | 0.52 | 0.28-0.96 | 0.035* |
| c) FATmax (%) | 0.99 | 0.92-1.06 | 0.774 |

*OR: odds ratio; 95% CI: confidence interval of 95%; $VO_{2max}$: maximal oxygen consumption; MFO: maximal fat oxidation rate.*
**p-value < 0.05. **Model adjusted by age and BMI.*

## DISCUSSION

The goal of the present study was to determine the protector role of cardiorespiratory fitness and exercise fat oxidation on IR in women with obesity or overweight. Statistically significant differences were found between both groups in $VO_{2max(\%)}$, which was lower in IR group (76.1% *versus* 83.2%; p = 0.015). At the same time, an association between $VO_{2max(\%)}$ and IR was found, which could indicate a possible protective role against the condition. It was determined that the increase in one unit of $VO_{2max(\%)}$ reduces the probability of presenting IR in an 8%. Although there are no studies that associate $VO_{2max}$ with IR, the results are consistent with previous studies that describe $VO_{2max}$ as a strong independent predictor of insulin sensitivity in non-diabetic subjects (18). In turn, this has been associated with glucose tolerance and HOMA2-IS in sedentary women with obesity (19) and with the presence of metabolic syndrome in overweight subjects (20). This has also been evidenced in adolescents with obesity, where a low $VO_{2max}$ was related to higher insulin indexes (HOMA-IR and insulin secretion in oral glucose tolerance test) (21). Similarly, Haufe et al. (22) found that in healthy subjects with obesity, those that had a greater $VO_{2max}$ were more sensitive to insulin, similar to that described by Messier et al. (23) and by Morris et al. (24) in postmenopausal women with obesity and in healthy subjects, respectively.

In regard to fat oxidation, no differences in FATmax were found between both groups, similar to the findings of Mogensen et al. (25) and Larsen et al. (26) in subjects with obesity with and without type 2 diabetes mellitus, and by Croci et al. in trained normal weight and overweight subjects (27). However it was observed that the IR group had a lower MFO than the Non-IR group (1.08 mg × kg$^{-1}$ × min$^{-1}$ *versus* 1.62 mg × kg$^{-1}$ × min$^{-1}$; p = 0.044). In turn, an association between MFO and IR was found that also could indicate a possible protective role against the condition.

As in the previous case, there are no studies that associate IR with MFO and they principally focus on the study of insulin sensitivity. In congruence with the results previously shown, Robinson et al. found a positive correlation between plasma insulin (28) and insulin sensitivity (29) with MFO in healthy young men.

Fat oxidation is strictly linked to mitochondrial oxidative capacity (30,31). At the same time, the mitochondrial metabolism has been related to IR (4,32). If we consider that $VO_{2max}$ and MFO are indirect and systemic clinical manifestations of muscular mitochondrial metabolism, it could be hypothesized that the present results might be due to a relation between mitochondrial metabolism and IR. It is necessary to mention the existence of some studies that have not found that relationship (33,34), including Lalia et al. (18) who showed a strong association between $VO_{2max}$ and IR, without finding an association between this last one and mitochondrial metabolism. Nevertheless, a correlation between $VO_{2max}$ and mitochondrial enzymatic content (35) and cytochrome c oxidase activity (36) has been described, which suggests a possible relation of the total quantity of mitochondrial respiration enzymes with oxidative muscular capacity and thus with total body oxidative capacity.

Previous researchers have evidenced an increase in MFO and $VO_{2max}$ through different types of training in subjects with IR and obesity (37). Studies related to the limitations of fatty acid utiliza-

tion in skeletal muscle during exercise are controversial, attributing it to enzymes and/or transporters involved in the translation of intermediate metabolites and to beta oxidation (38). Training has shown improvements in the function of all components involved in healthy subjects (38,39). Therefore, physical training has risen as one of the fundamental tools in the treatment of IR (40), but it is still not possible to determine which of the many parameters modified through exercise would have a greater impact on IR.

Currently, there is much divergence in the objectives and strategies of treatment in this patients profile, so the results of the present study could be useful in trying to define more accurate strategies on IR treatment. Future studies must evaluate the variation of $VO_{2max}$ and MFO and its impact in the improvements in insulin sensitivity and IR.

The principal limitation of this study is the utilization of HOMA-IR instead of hyperinsulinemic euglycemic clamp, which is considered the gold standard for the determination of IR. Another limitation of the study is the lack of a normal weight control group for contrasting the obtained results.

## CONCLUSION

This study demonstrated that $VO_{2max(\%)}$ and MFO present a protective role against IR. An increase of 1% in $VO_{2max(\%)}$ reduces the risk of IR in an 8%, whereas an increase of 1 $mg \times kg^{-1} \times min^{-1}$ in MFO reduces the risk of IR in a 48% in sedentary women with overweight or obesity. No association between FATmax and IR was found. Future studies should explain the mechanism by which an increase of $VO_{2max}$ and of MFO can improve insulin sensitivity (considering fatty acid transporters, enzymes and metabolic variables) and how these improvements could favor the treatment of IR.

## ETHICAL APPROVAL

This study was approved by the Scientific Ethics Committee (register 15-267). All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## INFORMED CONSENT

A waiver of the need to obtain informed consent was obtained from Scientific Ethics Committee.

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