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# Association of cardiorespiratory fitness with insulin sensitivity in overweight and obese postmenopausal women: a Montreal Ottawa New Emerging Team study

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**Abstract**

The purpose of this study was to examine the relation between insulin sensitivity and cardiorespiratory fitness in overweight and obese postmenopausal women. The study population consisted of 127 overweight and obese postmenopausal women (age, 57.7 ± 4.8 years; body mass index, 32.7 ± 4.7 kg/m$^2$). Subjects were classified by dividing the entire cohort into tertiles (T) based on insulin sensitivity expressed per kilograms of lean body mass (LBM) (T1, <10.9; T2, 10.9-12.9, T3, >12.9 mg/min per kilogram of LBM, respectively). Outcome measures were body composition (dual-energy x-ray absorptiometry), visceral adipose tissue (computed tomography), insulin sensitivity (hyperinsulinemic-euglycemic clamp), cardiorespiratory fitness (indirect calorimetry), lower-body muscle strength (1 maximal repetition), physical activity energy expenditure (doubly labeled water), fasting lipids, and inflammatory profile. We found a significant positive relationship between insulin sensitivity and cardiorespiratory fitness ($r$ = 0.25, $P$ = .005). Moreover, cardiorespiratory fitness was higher in the T3 group compared to the T1 group (36.2 ± 6.1 vs 33.1 ± 5.0 mL/kg LBM per minute, respectively; $P$ = .028). However, the difference was no longer significant after controlling for visceral adipose tissue or muscle strength. Finally, cardiorespiratory fitness was an independent predictor of insulin sensitivity. High levels of cardiorespiratory fitness are associated with higher levels of insulin sensitivity in overweight and obese postmenopausal women. Moreover, visceral adipose tissue accumulation or muscle strength may be potential mediators of this relationship.


## 1. Introduction

Insulin resistance is defined as a reduced insulin-stimulated whole-body glucose uptake [1]. Studies showed that insulin resistance is associated with an increased risk of type 2 diabetes mellitus and cardiovascular diseases [2-4]. Moreover, insulin resistance is now considered as a key component of the metabolic syndrome, which is a cluster of metabolic risks factors such as hyperglycemia, dyslipidemia, abdominal obesity, and hypertension [5-8]. Furthermore, previous studies showed that moderate to high levels of cardiorespiratory fitness (CRF) decreased the risk of developing the metabolic syndrome [9,10] and cardiovascular disease [11] in adults. In addition, CRF levels are significantly lower in type 2 diabetic patients than in healthy subjects [12]. Finally, recent studies reported that high levels of CRF are associated with lower insulin resistance (using surrogate indices) mostly in youth [13-17] and adults [3,18].

To our knowledge, the possible association between insulin sensitivity, using the hyperinsulinemic-euglycemic clamp technique, and CRF has not been fully examined in a well-characterized population of healthy sedentary, overweight, and obese postmenopausal women, a group at increased risk for developing type 2 diabetes mellitus [19]

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and cardiovascular disease [20]. Therefore, the purpose of this study was to investigate the relation between CRF and insulin sensitivity, using the gold-standard hyperinsulinemic-euglycemic clamp, in overweight and obese postmenopausal women. We hypothesized that insulin sensitivity would be positively associated with CRF. In addition, we examined potential confounding factors such as total fat mass, visceral fat, physical activity energy expenditure (PAEE), and muscle strength that may mediate the relationship between insulin sensitivity and CRF.

## 2. Methods

### 2.1. Subjects

The study sample consisted of 127 nondiabetic sedentary overweight and obese postmenopausal women aged between 46 and 70 years enrolled in the Montreal Ottawa New Emerging Team weight loss project. This study was approved by the University of Montreal ethics committee. One month before testing, weight stability within ±1 kg was verified by monitoring body weight for each subject on a weekly basis at our laboratory. Because of this weight stabilization, 4 subjects displayed a body mass index (BMI) slightly less than 27 kg/m$^2$ on testing day. Inclusion criteria and detailed methods for body composition, visceral fat, CRF, insulin sensitivity, blood profile, PAEE, and muscle strength were detailed in previous publications [21,22]. Briefly, women were included in the study if they met the following criteria: (1) cessation of menstruation for more than 1 year and a follicle-stimulating hormone level 30 U/L or higher, (2) sedentary for at least more than 3 months (<2 hours a week of structured exercise), (3) nonsmokers, (4) free of known inflammatory diseases, (5) no use of hormone replacement therapy, (6) BMI of 27 kg/m$^2$ or more. Moreover, on physical examination or biological testing, all participants had no history or evidence of cardiovascular diseases, peripheral vascular diseases or stroke, diabetes (fasting serum glucose <7.0 mmol/L and 2 hours post 75 g oral glucose tolerance test <11.0 mmol/L), orthopedic limitations, and medication that could affect cardiovascular function and/or metabolism.

### 2.2. Body composition

Body weight, lean body mass (LBM), and fat mass were measured using dual-energy x-ray absorptiometry (General Electric Lunar Corporation version 6.10.019, Madison, WI). Standing height was measured using a wall stadiometer (Perspective Enterprises, Portage, MI). Body mass index [body weight/height (m$^2$)] was calculated.

### 2.3. Computed tomography

A GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) was used to measure visceral adipose tissue. The subjects were examined in the supine position with both arms stretched above their head. The position of the scan was established at the L4 through L5 vertebral disk using a scout image of the body. Visceral adipose tissue area was quantified by delineating the intra-abdominal cavity at the internal most aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body.

### 2.4. Hyperinsulinemic-euglycemic clamp

The study began at 7:30 AM after a 12-hour overnight fast following the procedure described by DeFronzo et al [23]. An antecubital vein was cannulated for the infusion of 20% dextrose and insulin (Actrapid, Novo-Nordisk, Toronto, Canada). The other arm was cannulated for sampling of blood. Three basal samples of plasma glucose and insulin were taken over 40 minutes. Then, insulin infusion was initiated at the rate of 75 mU/m$^2$ per minute for 180 minutes. Plasma glucose was measured every 10 minutes with a glucose analyzer (Beckman Instruments, Fullerton, CA) and maintained at fasting level with a variable infusion rate of 20% dextrose. Glucose disposal was calculated as the mean rate of glucose infusion measured during the last 30 minutes of the clamp (steady state) and is expressed as milligram per minute per kilogram of LBM. Subjects were then characterized by dividing the entire cohort into tertiles (T) based on insulin sensitivity (<10.9 [T1] vs 10.9-12.9 [T2] vs >12.9 [T3] mg/min per kilogram of LBM, respectively).

### 2.5. Cardiorespiratory fitness ($Vo_{2peak}$)

Subjects performed a graded exercise test on an ergocycle Ergoline 900 (Ergoline, Bitz, Germany) to voluntary exhaustion. During the test, power output was increased by 25 W every 2 minutes. Peak $Vo_2$ (L/min) was considered to be the highest value obtained during the test. Expired gas was analyzed during the exercise protocol using an Ergocard (software version 6, MediSoft, Dinant, Belgium) cardiopulmonary exercise test station. Standard 12-lead electrocardiograms were performed at the end of every 2-minute stage. Three of the following criteria were required for a successful test: a respiratory exchange ratio above 1.1; heart rate within 10 beats per minute of maximal predicted heart rate value (220 − age); volitional cessation of exercise by the subject and a plateau in oxygen consumption for 60 seconds. Cardiorespiratory fitness was expressed as milliliter per kilogram of LBM per minute.

### 2.6. Doubly labeled water

Daily energy expenditure was determined from doubly labeled water over a 10-day period [24]. The doubly labeled water experiments generated 5 urine samples per study: a predose sample was collected before administration, 2 samples (16-24 hours later) were obtained after the $^2H_2^{18}O$ dose had initially equilibrated in the body, and 2 more samples were collected 10 days later. All samples were measured in triplicate for $^{18}O$-water and $^2H$-water. An Isoprime Stable Isotope Ratio Mass Spectrometer connected

to a Multiflow-Bio module for Isoprime and a Gilson 222XL Autosampler (GV Instruments, Manchester, UK) were used for daily energy expenditure measurements. Data processing was performed with MassLynx 3.6 software (Waters Corp, Milford, MA). Stability test was performed each day before testing giving a standard deviation of 0.026% for deuterium and 0.004% for $^{18}O$. In addition, resting metabolic rate was measured by indirect calorimetry as previously described [25]. Assuming a thermic effect of feeding of 10%, PAEE was then calculated from the following equation: PAEE = (total energy expenditure ×0.90) − resting metabolic rate.

Finally, 2-hour glucose was measured from an oral glucose tolerance test. After an overnight fast (12 hours), venous blood samples were collected for the measurement of serum concentrations of inflammatory markers and blood lipids. Lower-body muscle strength was assessed using leg-press weight-training equipment from Atlantis Precision Series (Atlantis Inc, Laval, Quebec, Canada).

### 2.7. Statistical analyses

The data are expressed as mean ± SD. We first verified the normality of the distribution of variables with a Kolmogorov-Smirnov test and found that triglycerides/high-density lipoprotein cholesterol (HDL-C) ratio, 2-hour glucose, and high sensitive C-reactive protein (hsCRP) were not normally distributed. Therefore, we used the log transformed values (base 10) for these variables in the analysis. Pearson correlations were first performed to examine the relationship between insulin sensitivity and CRF. Partial correlations were also used to control for total fat mass, visceral adipose tissue, PAEE, or muscle strength. Then, a 1-way ANOVA analysis was performed to compare mean differences among tertiles. When significant differences were found, a Tukey post hoc test was performed to identify group differences. An analysis of covariance was also used to control for total fat mass, visceral adipose tissue, PAEE, or muscle strength. Finally, a stepwise multilinear regression analysis was performed to identify predictors of insulin sensitivity. Based on exploratory analyses and using biologically plausible hypotheses, independent variables considered in the final model for insulin sensitivity were CRF, visceral adipose tissue, total cholesterol/HDL-C ratio, triglycerides/HDL-C ratio, hsCRP, 2-hour glucose, lower-body muscle strength, and PAEE. Statistical analysis was performed using SPSS for Windows (Chicago, IL). Significance was accepted at $P < .05$.

Table 1
Physical and metabolic characteristics of the 127 overweight and obese postmenopausal women

| Variables | Mean ± SD | Range |
|---|---|---|
| Age (y) | 57.7 ± 4.8 | 46.0-70.5 |
| BMI (kg/m$^2$) | 32.7 ± 4.7 | 26.1-48.5 |
| Body weight (kg) | 84.0 ± 13.8 | 56.4-130.4 |
| LBM (kg) | 42.5 ± 6.3 | 31.1-61.0 |
| Fat mass (kg) | 39.0 ± 9.2 | 23.8-73.1 |
| Fat mass (%) | 46.1 ± 4.6 | 36.5-57.9 |
| Visceral adipose tissue (cm$^2$) (n = 126) | 186.8 ± 54.9 | 83.6-345.6 |
| Insulin sensitivity (mg/min per kilogram of LBM) | 12.2 ± 3.3 | 4.9-24.3 |
| Total cholesterol/HDL-C | 3.8 ± 0.8 | 2.2-6.2 |
| Triglycerides/HDL-C | 1.2 ± 0.7 | 0.2-3.6 |
| Fasting glucose (mmol/L) | 5.2 ± 0.5 | 3.9-6.6 |
| 2-h glucose (mmol/L) | 6.3±1.8 | 3.4-10.9 |
| hsCRP (mg/L) (n = 126) | 3.3 ± 2.6 | 0.3-14.6 |
| CRF (mL/kg LBM per minute) | 34.8 ± 5.5 | 18.9-50.4 |
| CRF (mL/kg BW per minute) | 17.7 ± 3.1 | 8.8-25.3 |
| PAEE (kcal/d) (n = 125) | 926 ± 292 | 348-1697 |
| Lower-body muscle strength (kg/LBM) (n = 105) | 3.5 ± 0.9 | 1.8-6.3 |

Values are mean ± SD. BW indicates body weight.

Table 2
Pearson correlation coefficients ($r$ values) between insulin sensitivity as well as CRF with physical and metabolic characteristics

| Variables | Insulin sensitivity | CRF |
|---|---|---|
| Fat mass | −0.12 | −0.10 |
| Visceral adipose tissue | −0.32** | −0.34** |
| Total cholesterol/HDL-C | −0.27** | −0.02 |
| Triglycerides/HDL-C | −0.36** | −0.12 |
| 2-h glucose | −0.43** | −0.03 |
| hsCRP | −0.23** | −0.11 |
| PAEE | 0.10 | 0.06 |
| Lower-body muscle strength | 0.22* | 0.37** |

* $P < .05$.
** $P < .01$.

## 3. Results

Physical and metabolic characteristics of the 127 overweight and obese postmenopausal women are presented in Table 1. Pearson correlation coefficients between insulin sensitivity as well as CRF with physical and metabolic characteristics are presented in Table 2. A significant negative relationship was found between insulin sensitivity

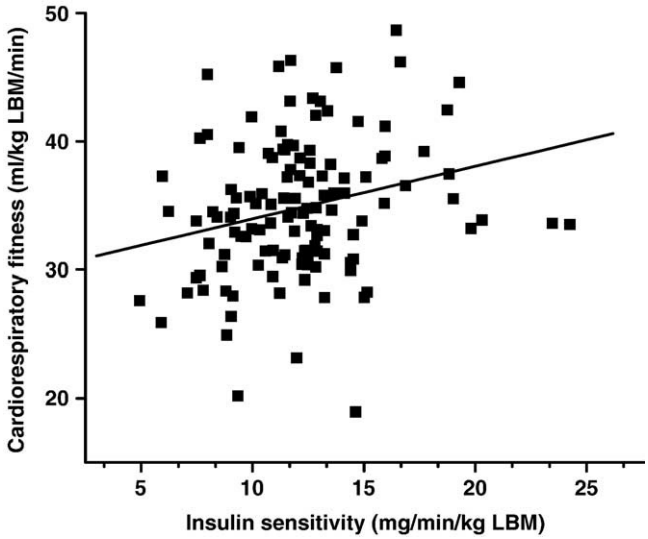


Fig. 1. Relationship between insulin sensitivity and CRF ($r = 0.25$; $P < .05$) in 127 overweight and obese postmenopausal women.

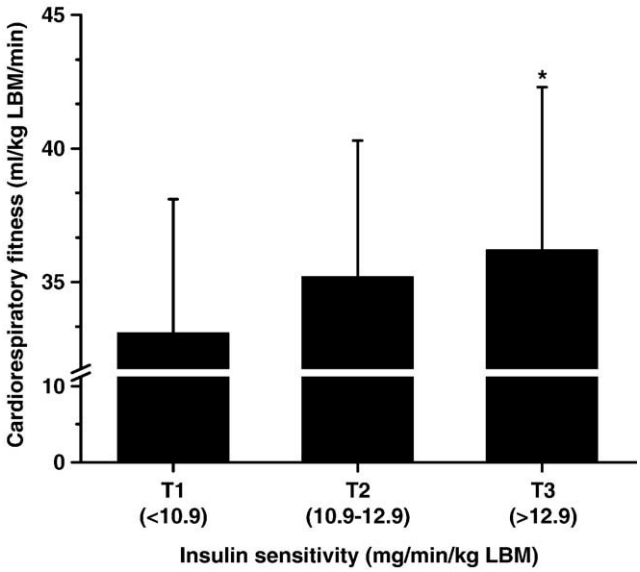


Fig. 2. Differences in cardioresporatory fitness in overweight and obese postmenopausal women classified into tertiles of insulin sensitivity. Values are mean ± SD. *Significantly different from the first (T1) tertile group.

and visceral adipose tissue ($r = -0.32$, $P = .001$), total cholesterol/HDL-C ($r = -0.27$, $P = .002$), triglycerides/HDL-C ($r = -0.36$, $P = .001$), 2-hour glucose ($r = -0.43$, $P = .001$), and hsCRP ($r = -0.23$, $P = .008$). Moreover, we found a significant correlation between muscle strength and insulin sensitivity ($r = 0.22$, $P = .023$). Furthermore, we observed that CRF was negatively associated with visceral adipose tissue ($r = -0.34$, $P = .001$) and positively correlated with muscle strength ($r = 0.37$, $P = .001$). However, PAEE and total fat mass were not associated with either insulin sensitivity or CRF.

Fig. 1 shows the significant and positive association between insulin sensitivity and CRF in our cohort ($r = 0.25$, $P = .005$). We also examined this relationship after controlling for visceral adipose tissue or muscle strength using partial correlation analysis. We found that the positive association between insulin sensitivity and CRF was no longer significant after controlling for visceral adipose tissue ($r = 0.16$, $P = .078$). However, the partial correlation between insulin sensitivity and CRF remained significant when adjusted for muscle strength, total fat mass, or PAEE.

Table 3
Metabolic parameters of the subjects classified into tertiles based on insulin sensitivity

| Metabolic parameters | T1 (<10.9) | T2 (10.9-12.9) | T3 (>12.9) |
|---|---|---|---|
| Fat mass (kg) | 40.5 ± 8.3 | 37.3 ± 9.5 | 39.2 ± 9.7 |
| Visceral adipose tissue ($cm^2$) | 213.3 ± 61.9 | 172.7 ± 43.4 * | 174.4 ± 49.1 * |
| PAEE (kcal/d) | 908 ± 264 | 901 ± 264 | 968 ± 341 |
| Lower-body muscle strength (kg/kg LBM) | 3.3 ± 0.8 | 3.5 ± 1.0 | 3.7 ± 0.9 |

Values are mean ± SD.
* $P = .002$ (significantly different from T1).

Table 4
Stepwise regression analysis regarding independent predictors of insulin sensitivity in overweight and obese postmenopausal women

| Dependent variable | Step | Independent variable | Partial $r^2$ | Total $r^2$ cumulative | $P$ |
|---|---|---|---|---|---|
| Insulin sensitivity (mg/min per kilogram of LBM) | 1 | 2-h glucose | 0.230 | 0.230 | .001 |
| | 2 | CRF | 0.075 | 0.305 | .003 |
| | 3 | Triglycerides/HDL | 0.055 | 0.360 | .004 |

Fig. 2 shows the differences in CRF in overweight and obese postmenopausal women classified into tertiles based on insulin sensitivity. We observed that CRF in the T3 group was significantly different from the T1 group (36.2 ± 6.1 vs 33.1 ± 5.0 mL/kg LBM per minute, $P = .028$). We also examined the differences in CRF after controlling for visceral adipose tissue or muscle strength using analysis of covariance. Significant differences in CRF between the 3 groups were abolished after adjusting for visceral adipose tissue or muscle strength. When the differences in CRF were adjusted for either total fat mass or PAEE, statistical significance still persisted among groups.

Metabolic parameters of the subjects classified into tertiles based on insulin sensitivity are shown in Table 3. No difference in fat mass, PAEE, and muscle strength was noted among the 3 groups. However, visceral fat content was significantly higher in the T1 group compared to the T2 and T3 group.

We performed stepwise regression analysis to identify independent predictors of insulin sensitivity. Table 4 illustrates the summary of the model. Our results showed that 2-hour glucose, CRF, and triglycerides/HDL-C ratio were independent predictors of insulin sensitivity, collectively explaining 36.0% of the variance.

## 4. Discussion

Results of the present study support our hypothesis. That is, we observed a significant positive relationship between insulin sensitivity and CRF. Furthermore, when subjects were characterized into tertiles based on insulin sensitivity, CRF was significantly higher in the third tertile group compared to the first tertile group. This could suggest that a high threshold of insulin sensitivity may be related to muscle adaptation associated with better CRF. This may also suggest that high CRF levels, despite similar large body fat content between groups, could contribute to a favorable metabolic profile (ie, insulin sensitivity). In support of this hypothesis, CRF was an independent predictor of insulin sensitivity in our cohort. These results are in line with the results of a recent study, which showed that peak oxygen uptake ($Vo_{2\ peak}$) was significantly correlated with insulin-adjusted glucose disposal rate and that $Vo_{2\ peak}$ was an independent predictor of insulin sensitivity in healthy young men [26]. Moreover, Seibaek et al [1] observed that $Vo_{2\ peak}$

was significantly associated with insulin-stimulated glucose disposal rate in adults with or without diabetes and ischemic heart disease. Furthermore, this study showed that $Vo_{2\ peak}$ was the only independent predictor of insulin sensitivity [1]. Finally, in the present study, it should be noted that CRF may be a better indicator of metabolic complications and thus stronger than PAEE and muscle strength as predictor of insulin sensitivity in our cohort. It should also be noted that the strength of the relationship between insulin sensitivity and CRF was reinforced by the fact that this relationship was present even in a homogenous population of overweight and obese postmenopausal women. That is, even within an overweight and obese population of similar body fat content, the relationship between insulin sensitivity and CRF was evident.

What is a potential mediator that could explain the relationship between insulin sensitivity and CRF? High levels of visceral fat have been associated with metabolic disturbances such as insulin resistance, dyslipidemia, and hypertension [27,28]. In addition, low levels of muscle strength are associated with metabolic complications [29,30] and an increased risk of mortality [31,32]. In the present study, we observed a significant relationship between visceral fat with insulin sensitivity and CRF. Moreover, we reported a significant correlation between muscle strength with insulin sensitivity and CRF. Finally, we showed that statistical control for visceral fat or muscle strength (but not total body fatness or PAEE) abolished the differences in CRF among individuals categorized for severity of insulin sensitivity. This suggests that the relationship between insulin sensitivity and CRF could be, at least in part, mediated by visceral adipose tissue or muscle strength. Although this finding is not totally surprising, this potentially underscores the importance of visceral fat or muscle strength as modulating factors influencing the relationship between insulin sensitivity and CRF. That is, even in the presence of large quantities of fat mass, visceral fat and muscle strength emerged as the only variables that effectively abolished differences in CRF in overweight and obese postmenopausal women. Accordingly, Gerson and Braun [3] examined the effect of high CRF and high body fat on insulin sensitivity. This study showed that insulin sensitivity was lower in unfit obese subjects than in fit obese individuals. However, unfit obese subjects had significantly more abdominal fat compared to fit obese individuals. Therefore, the authors concluded that lower levels of abdominal fat in the fit obese group could partially explain their higher levels of insulin sensitivity [3]. However, 2 studies conducted in children observed that the positive association between insulin sensitivity and CRF was no longer significant after controlling for fat mass and soft lean tissue mass [13] or percentage of body fat [17]. Finally, leptin has been shown to be correlated with visceral adipose tissue [33]. Furthermore, high levels of leptin have been associated with insulin resistance [34]. Therefore, leptin could also be a potential mediator of the association between insulin sensitivity and CRF and serve as a substitute for the assessment of visceral fat. However, further studies are needed to confirm this hypothesis.

The present study has some limitations. First, our cohort is composed of nondiabetic sedentary overweight and obese postmenopausal women. Thus, our findings are limited to this population. Second, we used a cross-sectional approach, which does not allow us to draw conclusions as to causal associations between insulin sensitivity and CRF. Despite these limitations, our results are strengthened by using gold-standard techniques to measure insulin sensitivity, body composition, and CRF in a relatively large sample size of well-characterized overweight and obese postmenopausal women.

In conclusion, results of the present study show that high levels of CRF were associated with high levels of insulin sensitivity in sedentary overweight and obese postmenopausal women. However, this relationship was abolished after adjusting for visceral adipose tissue or muscle strength, suggesting that the relation between CRF and insulin sensitivity could be mediated, at least in part, by visceral adipose or muscle strength.

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