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Influence of Body Composition on Cardiorespiratory Fitness and Metabolic Markers in Physically Inactive Individuals with Insulin Resistance: An Observational Study

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Abstract: The aim of this study was to determine body composition influence on cardiorespiratory fitness and metabolic markers in physically inactive individuals with insulin resistance (IR). Nineteen overweight and obese (body mass index [BMI] 25.0–29.9 kg·m^{-2}; ≥ 30.0 kg·m^{-2}, respectively) patients diagnosed with IR (5 men and 14 women; age: 32.74 ± 10.07 years; BMI: 32.5 ± 4.60 kg·m^{-2}). The body composition included BMI, fat mass, and fat-free mass. Cardiorespiratory fitness was measured by maximal oxygen uptake (VO_2max). Metabolic markers included maximal fat oxidation, fasting glucose, and insulin. IR was determined by homeostatic model assessment (HOMA-IR). The results of the partial correlations (i.e., body mass, age, and sex) reported that fat-free mass, fat mass, and BMI were significantly correlated with VO_2max. Additionally, the multiple linear regression model indicated that fat-free mass and BMI explained the variance of VO_2max by 89%. However, no substantial correlations were reported between fat mass or fat-free mass with HOMA-IR, fasting glucose, or insulin. This study concluded that a higher percentage of fat-free mass and lower BMI is positively related to better cardiorespiratory fitness despite the IR status of the participants analyzed.

Keywords: overweight; obesity; body composition; fitness; insulin resistance

1. Introduction

Insulin resistance (IR) is a metabolic condition considered the main etiological factor in the development of Type 2 diabetes [1]. One of its characteristics is that, although it is not deadly, it is associated with several detrimental cardiometabolic risk factors, such as hypertension, hepatic steatosis, dyslipidemia, glucose intolerance, and hyperinsulinemia [1,2]. In turn, IR is commonly associated with excess body fat (overweight/obesity) and sarcopenia (i.e., muscle mass loss and strength) [3,4]. This loss of functionality and body composition characteristics is aggravated because, in this condition, individuals have an increased insulin resistance index (HOMA-IR) and, therefore, a lower insulin sensitivity, increasing the risk of IR development [4,5]. Furthermore, IR is related to reduced cardiorespiratory fitness (VO_2max), as it is inversely correlated with HOMA-IR and metabolic inflexibility to oxidize fat (Maximal fat oxidation or MFO) [6–10].

In this context, the assessment of body composition appears to be important for the prevention or progression of IR [11,12]. Specifically, excess body fat plays a detrimental role in glucose metabolism [13], whereas greater fat-free mass or lean tissue (FFM) is attributed to a protective role and healthy metabolic profile due to a metabolically active tissue and allows for the uptake of 80% of insulin-stimulated glucose in the body [14–16]. These components can be determined by dual-energy X-ray absorptiometry (DXA) or bioelectrical multifrequency impedance analysis (BIA), a low-cost alternative technique that allows the estimation of potential health risks [17,18].

Accordingly, the relationship between body composition with VO_2max, HOMA-IR, and MFO remains controversial. Mondal and Mishra [19] showed a significant inverse correlation between body fat percentage and VO_2max in healthy young adults (men n = 30; women n = 24; age range = 18–25 years) and a positive correlation between FFM with VO_2max [19]. However, according to the authors' knowledge, there are limited studies on the contribution of body composition to MFO in IR individuals. [20,21]. In a recently published systematic review, Arad et al. [21] concluded that, in most articles, there was no influence of overweight/obesity on MFO during exercise, although there were conflicting results (8 of 24 articles) [21]. In turn, they mentioned that factors other than body fat (e.g., muscle mitochondrial sparsity) may influence MFO during exercise [21]. Other correlational studies between body composition with VO_2max and MFO indicate contradictory results. [20,22]. For example, Blaize et al. [20], in young (n = 14) healthy and active (21–31 years) women (n = 14), found no significant correlations between FM and FFM with MFO or VO_2max [20]. Meanwhile, Croci et al. [22] reported no substantial relationship between fat mass percentage (FM%) and MFO in normal weight (n = 12; 17.2 ± 5.7 FM%) and overweight (n = 12; 30.0 ± 5.3 FM%) recreationally trained men with equivalent cardiorespiratory fitness (VO_2max 39.0 ± 5.5 vs. 41.4 ± 7.6 mL.kg·min^{-1}).

Consequently, more research is needed to corroborate the contribution of body composition on cardiorespiratory fitness and metabolic markers (i.e., MFO; HOMA-IR; insulin) related to the development or prevention of IR. Therefore, this study aimed to determine the body composition influence on cardiorespiratory fitness and metabolic markers in physically inactive individuals with IR.

2. Materials and Methods

2.1. Participants

A priori, the required sample size was determined using the G*Power program (version 3.1.9.6, Franz Faul, Universiät Kiel, Kiel, Germany) and based on a study with similar characteristics [19]. The statistical power analysis performed included the following variables: r = 0.73; alpha error: 0.05 and desired power (1-β error): 0.80. The results of the analysis indicated that a number of 11 participants would be necessary to obtain statistical significance between the correlation between fat-free mass and VO_2max. The study procedures were following the Helsinki Declaration of Ethics for Human Medical Research [23]. The Local Ethics Committee approved the study protocol (register number 151007005). This protocol can be made available at reasonable request. Participants must be overweight (≥25.0–29.9 kg·m^{-2}) or obese (≥30.0 kg·m^{-2}) and physically inactive according to World Health Organization's guidelines [24]. Patients were exempted from consuming any type of drug or drug treatment or dietary supplements that affect metabolism and substrate kinetics. They were also excluded if they declared themselves smokers. According to the criteria, the study was able to consider the information of 19 patients from the database of an Obesity Treatment Center.

Sample characteristics are described in Table 1.

Table 1. Descriptive characteristics of the participants analyzed (n = 19).

Variables	Mean	DS	Lower to	Upper 95%CI
Age (years)	32.74	10.07	27.88 to	37.59
Height (cm)	164.2	7.966	160.3 to	168.0
Body mass (kg)	88.01	14.87	80.84 to	95.1
BMI ($kg \cdot m^{-2}$)	32.54	4.603	30.32 to	34.76
FM (%)	38.01	9.551	33.41 to	42.61
FFM (%)	50.00	10.85	44.77 to	55.23
HOMA-IR	3.537	0.8584	3.123 to	3.951
Fasting insulin ($mg \cdot dL^{-1}$)	16.54	3.487	14.86 to	18.22
Fasting glycemia ($mg \cdot dL^{-1}$)	86.42	6.301	83.38 to	89.46
VO_2max ($L \cdot min^{-1}$)	2.021	0.6844	1.691 to	2.351
MFO ($g \cdot h^{-1}$)	6.021	5.410	3.414 to	8.628

Abbreviation: DS: Standard Dev CI: confidence interval; BMI: Body Mass Index. HOMA-IR: Insulin Resistance Index. VO_2max: Maximal oxygen uptake. FM: Fat mass. FFM: Free-fat mass. MFO: maximal fat oxidation.

2.2. Measurements

2.2.1. Body Composition

Participants arrived in the laboratory after more than 6 h of fasting. None of the women participants came to assess during the menstrual phase. The height and weight were measured with an accelerometer and digital scale (SECA 217, Hamburg, Germany, accuracy 0.5 cm and 0.1 kg, respectively). Both assessments were conducted without shoes and with light clothes. FFM and FM percentage, and body mass were assessed using a validated bioimpedance system (Inbody 720, Seoul, Korea) with tetrapolar multifrequency (8 contact points) [25].

2.2.2. Insulin Sensitivity

Insulin sensitivity was measured by the insulin resistance index (HOMA-IR) [24]. HOMA-IR was calculated as fasting insulin × fasting glucose/405. HOMA-IR is a validated method (through glucose-high cholesterol clamps) that is considered the gold standard for IR assessment and is often used for IR and type 2 diabetes clinical diagnosis [26,27]. Based on a previous study with participants from the same country [28], the HOMA-IR score was 2.5 to 5.0 to classify participants with IR.

2.2.3. Cardiorespiratory Fitness

Cardiorespiratory fitness was conducted by an incremental test of a bicycle ergometer (Technogym Bike Med, Technogym, Gambettola, Italy) according to previous recommendations [29]. The theoretical maximum load (W) was estimated [30]. The protocol consisted of a 3-min rest period; a 3-min warm-up at 20% of the maximum load; followed by 6-min stages at 30, 40, 50, and 60% of the maximum load up to a respiratory exchange ratio ≥ 1. Thereafter, 6-min stages were completed until the maximum effort was reached. Verbal stimuli were allowed. The test was considered maximal if a respiratory exchange ratio ≥ 1.1 was reached and/or if the maximum heart rate (HRmax) was greater than or equal to the theoretical maximum predicted by the Morris equation for the cycloergometer test.

The protocol consists of a 3-min rest period; a 3-min warm-up at 20% of the maximum load; followed by 6-min phases at 30, 40, 50, and 60% of the maximum load up to a respiratory exchange ratio of ≥ 1. Afterwards, the 6-min stages were completed until the maximum effort was achieved. Verbal stimuli were permitted. The test is considered to be the maximum if the respiratory exchange rate of 1.1 is reached and/or the maximum heart rate (HRmax) exceeds or is equal to the theoretical maximum predicted by the Morris equation for the cycloergometer test [31]. Following the manufacturer's specifications, taking into account the last phase of the cycloergometer, the following variables are calculated from the average of the last 30 s of air inhaled using a breath-by-breath gas analysis method (Metalyzer 3B-R2. Cortex®, Leipzig, Germany): ventilatory threshold 2 (value provided by MetaSoft® Studio software (company: Cortex®, Leipzig, Germany),

and HRmax (beats·min^{-1}), maximum load (watts). The same methodology was used to determine VO_2max (L·min^{-1}).

2.3. Procedures

Measurements were performed on two days. On the first day fasting glucose and insulin and body composition were measured and on the second day VO_2max, and MFO. The doctor responsible for the patient measured fasting glucose and insulin, while the body composition and metabolic tests (MFO and VO_2max) were conducted by the physiotherapist responsible at the treatment center. All tests were conducted under similar environmental conditions (21–23 °C) at the same time between 08 h and 10 h to minimize the circadian rhythms impact [32].

2.4. Statistical Analysis

The data were processed in SPSS version 23 (Microsoft Corp., Redmond, WA, USA) and presented as a mean ± standard deviation (SD) with a 95% confidence interval (95% CI). Normal distribution was verified using the Shapiro–Wilk test. The relationship between body composition and on metabolic and cardiorespiratory markers was analyzed using partial correlations. The model included the covariates body mass, age and sex. The correlations were interpreted as 0 to 0.30 (small), 0.31 to 0.49 (moderate), 0.50 to 0.69 (large), 0.70 to 0.89 (very large) and 0.90 to 1.0 (approximately perfect to perfect) [33]. Afterward, only significant variables were included in a forward step-by-step multi-regression analysis. Independence variables were analyzed by a one-way analysis of variance (ANOVA) [34]. A residuals analysis was used to detect outliers (Maloney et al., 2017). The collinearity between predictor variables was examined with the variance inflation factor (VIF) and the tolerance factor and verified with the Durbin–Watson test [35].

3. Results

Correlations between Analyzed Outcomes

Table 2 describes the partial correlation results. The main results showed a significant correlation between FFM, FM, and BMI with maximal oxygen uptake (r = 0.53, $p = 0.034$; $r = -0.53$, $p = 0.034$; $r = -0.75$, $p < 0.001$; respectively). In addition, the results of the multiple linear regression model showed that fat-free mass and BMI influenced the variance of VO_2max by 89%.

Table 2. Correlation between body composition components and metabolic variables of physically inactive individuals with IR.

Variables	VO_2max	Fasting Insulin	Fasting Glycemia	HOMA-IR	MFO
BMI (kg·m^{-2})	−0.75 **; (−0.90 to 015); 0.001	0.34; (−0.21 to 0.74); 0.18	0.30; (−0.26 to 0.75); 0.25	0.44; (−0.07 to 0.78); 0.08	−0.33; (−0.74 to 0.48); 0.20
FM (%)	−0.53 *; (−0.83 to 0.22); 0.03	0.15; (−0.41 to 0.56); 0.58	0.15; (−0.49 to 0.65); 0.55	0.23; (−0.39 to 0.59); 0.39	−0.04; (−0.59 to 0.82); 0.86
FFM (%)	0.53 *; (0.22 to 0.83); 0.03	−0.15; (−0.56 to 0.41); 0.58	0.15; (−0.65 to 0.49); 0.55	−0.23; (−0.59 to 0.39); 0.39	−0.04; (−0.82 to 0.59); 0.86

Values are reported as correlation; (lower to upper 95% CI); p value. BMI: Body Mass Index. FM: fat mass; FFM: free-fat mass; HOMA-IR: insulin resistance index. VO_2max: maximal oxygen uptake; MFO: maximal fat oxidation. *: denotes $p < 0.05$. **: denote $p < 0.001$.

Also, low and moderate correlations were reported between FM%, FFM, and BMI with Insulin and HOMA-IR.

4. Discussion

The aim of this study was to determine the influence of body composition on cardiorespiratory fitness and metabolic markers in physically inactive individuals with insulin resistance. The main results showed a significant correlation between FFM, BMI, and FM with VO_2max, independent of age and sex. In addition, the multiple linear regression model showed that BMI and fat-free mass influenced the variance of VO_2max by 89%.

In addition, low to moderate, but not significant, correlations were observed between BMI, %FM and FFM with HOMA-IR and fasting blood glucose.

Regarding the results of the relationship between body composition and VO_2max Blaize et al. [20] found no significant correlations between FM and FFM with VO_2max in young (n = 14) healthy and active (21–31 years) women [20]. These differences could be attributed to the heterogeneity of the sample (5 men and 14 women) of physically inactive adults (32.7 ± 10 years) with IR. In this sense, the contrast of our results could be explained by the fact that physically inactive people with IR have a low VO_2max [6–10] and a decrease in the number of mitochondria [36] during exercise or at rest [36]. This impaired in their ability to capture and transport oxygen in the cardiorespiratory system and the ability to capture oxygen in skeletal muscle by mitochondria [37,38]. Indeed, this leads to a decrease in mitochondrial fatty acid oxidation by increasing intracellular levels of fatty acyl-CoA and diacylglycerol, inhibiting PI3-kinase activity and causing suppression of insulin-stimulated glucose transport [36,38]. Therefore, there is a close relationship between decreased cardiorespiratory fitness with decreased fat oxidation and the development of IR [8–10].

In accordance with the above, however, we did not find a relationship between body composition and MFO. In this regard, Croci et al. [22] studied the relationship between anthropometric characteristics and MFO by comparing men with normal weight (n = 12; 17.2 ± 5.7 FM%) and overweight (n = 12; 30.0 ± 5.3%FM) recreationally trained matched in cardiorespiratory fitness (VO_2max 39.0 ± 5.5 vs. 41.4 ± 7.6 mL·kg·min^{-1}; p = 0.31) and age (p = 0.93). Among the results, as in our results, they found no correlations between FM, FFM, and BMI ($p > 0.05$) with MFO. These results could be explained by the fact that in both obese and lean individuals, IR states are characterized by inefficient utilization of energy substrates (metabolic flexibility), both glucose and fat, instead of fatty acid absorption favoring triglyceride accumulation in skeletal muscles [7]. Furthermore, as demonstrated in the study by Kelley et al. [39], intermyofibrillar mitonchondria size, electron transport chain activity, and insulin sensitivity are related to IR [39]. Therefore, VO_2max, as described by Croci et al. [22], may be an independent indicator of body weight and fat mass in the development of IR in an overweight or obese state.

On the other hand, it is well accepted that a high percentage of FM or BMI and a low percentage of FFM increases the risk of developing IR [40,41]. However, whether or not IR develops will also depend on the distribution and location of body fat, i.e., where it accumulates. Accumulation of visceral adipose tissue, muscle intracellular fat deposition, or, in particular, intrahepatic lipid accumulation has been identified as contributing to or potentially triggering IR [40,41]. Consistent with the above, Zhang et al. [42] reported correlations of different adipose tissue depots/obesity indices with IR according to HOMA-IR. Specifically, the authors showed a significant correlation between HOMA-IR and FM (r = 0.49, 95% CI 0.407 to 0.570) and BMI (r = 0.48, 95% CI 0.44 to 0.51) [42]. Our results revealed similar results although our correlations were low to moderate, not significant, between the percentage of FFM, FM, and BMI with HOMA-IR. Therefore, body composition analyses such as BMI, FM and FFM may be independently indicative of the metabolic health of people with IR who are physically inactive. Regarding BMI, despite the questions about its use due to its limited representativeness of body adiposity and/or muscle mass, it is still one of the preferred measures in clinical practice [12], although we recommend the use of FM and FFM which better represents metabolically active tissues [16]. Therefore, the use of different, mainly low-cost technologies, such as bioelectrical impedance to analyze body composition, could be more useful in the field to address the prevalence of IR and type 2 diabetes. In fact, FFM percenteage could serve as a proxy indicator of VO_2max independently of age and sex in the development or risk of developing IR.

5. Limitations

Observational studies are not without limitations. In this aspect, the limited sample size, which may have affected the results of the analyses. However, it is pertinent to note

that this is a study with participant characteristics (overweight or obese IR) that are difficult to study.

Therefore, future studies should confirm or disconfirm our results. This would involve using DXA to analyze whether the fat distribution could indeed moderate the relationship with the metabolic markers analyzed.

6. Conclusions

This study concluded that a higher FFM and an appropriate BMI would be related to better cardiorespiratory fitness despite the IR condition. No significant correlations were reported between fat-free mass and fat mass with the metabolic markers analyzed.

Author Contributions: J.A.-G., A.O.-A. and J.M.G.-G. conceived the idea of the study. J.A.-G. and L.G.-R. participated in the data collection procedures. J.A.-G. and A.O.-A. performed the formal analysis and/or interpretation of the data. J.A.-G., A.O.-A. and E.B.-S.M. wrote the initial draft of the manuscript. J.M.G.-G., E.B.-S.M., V.C.-U., M.A.C.C. and L.G.-R. reviewed the paper. All authors have read and agreed to the published version of the manuscript.

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