International Journal of Nutrition and Metabolism Vol. 3(7), pp. 90-96, August 2011
Available online http://www.academicjournals.org/ijnam
ISSN 2141-2499 ©2011 Academic Journals

Full Length Research Paper

Nutritional and metabolic risk factors for insulin resistance in adults

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Accepted 21 July, 2011

The purpose of this study is to investigate the association of insulin resistance (IR) with dietary, fitness, anthropometric and other components of Metabolic Syndrome (MS) in adult participants. Cross-sectional study of 80 adult participants (58±8 years old) were clinically and ethically selected. They were all assessed for anthropometry, dietary habits, plasma biochemistry and indirect measurement of maximal oxygen uptake (VO_2max). Participants were diagnosed for MS by IDF criterion and placed in 3 different groups using tertiles of HOMA-IR. Values were statistically correlated with the remaining variables. Predictors of IR were determined by multivariate regression analysis. HOMA-IR was significant ($p<0.001$) and positively associated with MS prevalence (r=0.67), C-reactive protein (r=0.58), waist circumference (WC) (r=0.55), servings of fat consumption (r=0.52), body weight (r=0.43), body mass index (r=0.40), uric acid (r=0.40), inversely correlated associated with HDL-c (r=-0.56), VO_2max (r=-0.28), ingested fibers (r=-0.47) and fruits (r=-0.39). The fiber intake discriminated tertiles of HOMA-IR (G1<G2<G3). The variables considered independent predictors of HOMA-IR were WC, fat intake, MS, low fiber intake, low muscle mass and high plasmatic concentrations of uric acid. The highest values of HOMA-IR (P75) were positively associated with consumption of refined grains, uric acid, triglycerides, low consumption of fruit and low HDL-c. Main determinants of IR are preventable factors.

Key words: Insulin resistance, oxidative stress, inflammation, lipoproteins, eating habits, physical fitness.

INTRODUCTION

Studies indicate the intracellular accumulation of fatty acids and/or inflammation and oxidative stress as causes of lower translocation of Glut4 to the cell membrane, and consequently lower blood glucose removal (Samuel et al., 2010).

The abnormal accumulation of triglycerides in the cell (that lead to non-alcoholic steatohepatitis and myosteatosis) is due to the imbalance captation-synthesis/ oxidation free fatty acids that have diet and exercise (muscle work) as modulators (Solomon et al., 2009; Naples et al., 2010)

The consequence of physical inactivity, poor diet and obesity is the development of insulin resistance (IR) and dyslipidemia, resulting in oxidative and inflammatory stress (Sies et al., 2005). The increase in adipose tissue induces systemic inflammation due to secretion of proinflammatory factors by adipocytes. These bioactive substances are known to exert a variety of effects on glucose and lipid metabolism (Mangge et al., 2010). Furthermore, chronic inflammation is a key feature of metabolic syndrome (MS) (Monteiro and Azevedo, 2010).

High consumption of saturated fats and lower in fibers, vegetables and fruits can influence the blood glucose by promoting the positive energy balance and increasing coagulation factors, inflammatory and oxidative stress (Liese et al., 2009). In parallel, the mild-moderate exercise increases insulin sensitivity and beta-oxidation of fatty acids preventing their intracellular accumulation (Solomon et al., 2009).

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Different authors claim that changes in lifestyle, such as adherence to healthy eating habits and regular exercise are essential in preventing and treating the majority of the non-transmissible chronic diseases. These interactions promote behaviors that prevent or at least reduce the state of IR and can delay the onset of DM2 (Horton, 2009; Belalcazar et al., 2010).

Scientific studies showed that several strategies of lifestyle change can reduce, in part, the incidence of DM2 and its complications (Weickert et al., 2006; Solomon et al., 2009; Naples et al., 2010; Belalcazar et al., 2010). However, an intervention with all indicators related to IR would increase the dropout of program by patients (Pi-Sunyer, 2007). Therefore, knowing the main indicators associated with IR is important to design effective strategies and promote the adherence of patients. The aim of this study is to investigate the association of IR with anthropometric, dietary, biochemical and physical (aerobic and muscular fitness).

METHODOLOGY

A cross sectional study was developed with adults clinically selected to participate in a lifestyle change program. Eighty participants were included in accordance with the following criteria: older than 40 year, not in use of vitamins, supplements or medicines which may alter insulin actions. The participants signed a consent form approved by the ethics committee of the State University of São Paulo.

We evaluated 34 variables possibly involved in IR (6 clinical, 5 anthropometric, 6 dietetics, 2 physical and 15 biochemical). The body composition evaluation consisted of waist circumference and body mass index (BMI) using weight and height according to WHO recommendations (2002). Body fat (Segal, 1988) and muscle mass (Janssen et al., 2000) were determined by electrical bioimpedance (Quantum BIA-101Q, Clinton Township). Normal values of body fat percentage were considered 15 to 25% for males and 20 to 35% for females (Bray, 1992). Sarcopenia was defined when the percentage of muscle mass was ≤37% for males and ≤28% for females (Janssen et al., 2002).

Blood pressure measurement was made using a digital sphygmomanometer (OMRON model HEM-413C) following the recommendations of National Cholesterol Education Program's Adult Treatment Panel III (2001).

Food intake was estimated by 24 h recall questionnaire, calculated using the program for nutritional analysis NutWin® and the numbers of servings consumed were adjusted into servings according to the Brazilian adapted food pyramid (Mota et al., 2008). Dietary reference intakes for fatty acids, cholesterol and fibers were determinate according to WHO (2003).

The maximal oxygen uptake (VO_2max) was determined individually through the maximal test protocol Balke and Ware (1959) and the American Heart Association values were utilized as reference (Gibbons et al., 1997). The palmar grip strength was evaluated using JAMAR® dynamometer and establishing an adjustment index obtained by dividing between the quantities of strength measured in kilograms by absolute total fat:

Real strength= strength (kg)/ absolute total fat (kg)

This index was proposed by our group, because obese individuals had greater strength, and thus a positive correlation with IR. Similar correction was performed by another study that divided the palmar grip strength by body weight of studied participants (Jurca et al., 2005). The participants were classified according to tertiles of real strength.

Blood samples obtained after 12 h of overnight fasting were used for measurements of plasma glucose, uric acid, triglycerides, total and HDL-cholesterol calorimetrically in an automatic analyzer (System Vitros chemistry 950 Xrl, Johnson and Johnson). LDL-cholesterol was calculated using Friedewald's formula (Friedewald et al., 1972). The values used as reference were determined by the National Cholesterol Education Program's Adult Treatment Panel III (Pearson et al., 2003). The ultra-sensitive C-reactive protein and insulin were assayed by quimioluminescence (Immulite) and plasma homocysteine by HPLC (Shimadzu).

The diagnosis of MS followed the International Diabetes Federation (Alberti et al., 2006). Insulin resistance was estimated through homeostatic model assessment-insulin resistance (HOMA-IR) (Levy et al., 1998). Additionally were calculated homeostatic model assessment-β cell function (HOMA-β), quantitative insulin sensitivity check index (QUICKI) and index of peripheral insulin sensitivity (McAuley) (Levy et al., 1998; Acaso et al., 2003).

Participants were distributed into tertiles of HOMA-IR values according to the degree of IR (G1, G2 and G3) and these groups were differentiated by either parametric (ANOVA/MANOVA) or non-parametric (Kruskall Wallis) tests. G1: HOMA-IR below 0.98 (n=20), G2: HOMA-IR between 0.98 and 2.50 (n=40), G3: HOMA-IR up to 2.50 (n=20). The relationship between HOMA-IR and another variable was tested using Spearman's rank test. Logistic regression was used to obtain adjusted odds ratio for P75 HOMA-IR (> 2.50) and the variables analyzed were dichotomized in normal and altered. Subsequently, the risk factors-insulin resistance (log HOMA-IR) association was evaluated using multivariate logistic regression. Statistical analysis was done using SPSS version 12.0 for windows, and statistical significance set at $p<0.05$.

RESULTS

Female was predominant in the sample studied (70%). The mean age of participants was 58±8 years old, 72.5% were obese or overweight and 55% had waist circumference levels above normal. Half the participants were classified as having the MS and 51.3% as sarcopenic (Table 1).

Insulin resistance was associated with greater insulin secretion calculated by HOMA-β ($r=0.64$; $p<0.00001$). In contrast, there was a decrease in the QUICKI and McAuley indexes ($r=-1.0$, $r=-0.84$; $p<0.00001$, respectively), confirming the diagnosis of IR.

Higher HOMA-IR tertile (G3>2.50) was characterized by greater weight (85.8±6.0 vs. 70.7±6.7 and 71.5±7, $p<0.01$), body mass index (32.2±1.5 vs. 26.2 + 2.2 and 26.7±2.2, $p<0.001$), waist circumference (107.1±12.4 vs. 92.3±8.6 and 89.6±9.2, $p<0.001$) and body fat percentage (43.8±6.0 vs. 28.7±2.2 and 27.3±4.6; $p<0.01$) compared to G2 and G1, respectively. In the analysis of food intake, G3 had lower consumption of fruit (2.5±1.6 vs. 4.8±2.3 and 5.5±2.3; $p<0.01$) and dietary fibers (11.8±6.7 vs. 18.2±6.8 and 22.4±8.4; $p<0.001$), as well as higher consumption of refined cereals (5.0±1.1 vs. 3.0±0.8 and 2.8±1.0; $p=0.01$), meat servings (2.0±0.5 vs. 1.0±0.69 and 1.25±0.44; $p=0.03$) and fat servings (2.8±1.0 vs. 1.5±0.6 and 1.0±0.8; $p=0.001$) as compared to G2 and G1 (Figure 1).

G3 showed higher concentrations of triglycerides

Table 1. Prevalence of anthropometric alterations and metabolic syndrome.

Anthropometric alterations	Total (%)	Men (%)	Women (%)
Overweight	38.8	41.9	58.1
Obesity	33.7	22.2	77.8
High waist circumference	55.0	22.7	77.3
Sarcopenia	51.3	41.7	55.4
Metabolic syndrome	50.0	70.0	30.0

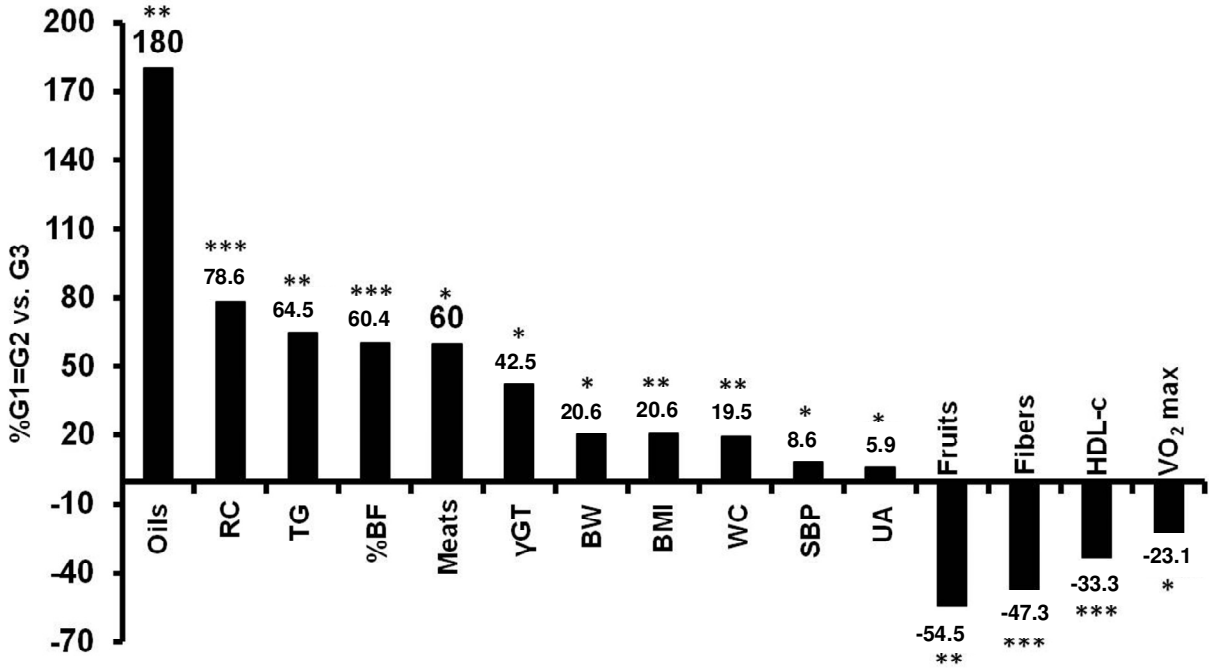

Figure 1. Magnitude of difference (%) between the higher (G3) against the lower (G1=G2) HOMA-IR groups.
Oils: servings of oil intake; RC: refined cereal; TG: plasma triglycerides; %BF: %of body fat; Meats: servings of meats intake; γGT: plasma γ glutamil transpeptidase activity; BW: body weight; BMI: body-mass index; WC: waist circumference; SBP: systolic blood pressure; UA: plasma uric acid; Fruits: servings of fruits intake; HDL-c: plasma HDL-cholesterol; VO_2max: aerobic capacity *p<0.05, **p<0.01, ***p<0.001.

(178.5±38.1 vs. 130±36.8 and 108.5±28 mg/dL; p=0.001), uric acid (5.4±1.4 vs. 4.9±1.2 and 5.1±1.4 mg/dL; p=0.04), γ glutamyl transferase (28.5±8.5 vs 22±5.2 and 20±5.3mg/dL; p=0.01) and hs-CRP (5.9±2.3 vs. 2.0±1.1 and 0.9±0.6mg/L; p<0.001) and lower concentrations of HDL-cholesterol (39.0±44 vs. 52.5±7.4 and 58.5±8.7 mg/dL; p=0.001), compared to G2 and G1, respectively (Figure 1). Systolic blood pressure was higher in G3 group (8.6%; p=0.02). Real strength (0.88±0.40 vs. 1.46±0.29 and 1.48±0.96 kg; p=0.01) and maximal oxygen uptake (23.3±6.4 vs. 27.7±7.0 and 30.3±8.7 mL/kg/min; p=0.01) was lower in G3 compared to G2 and G1, respectively (Figure 1).

HOMA-IR was positively (p<0.01) associated with body weight, BMI, waist circumference, body fat percentage and inversely associated with muscle mass (Figure 2). Regarding dietary variables represented by servings of refined cereals, meat, oils, percentage of total dietary fat and saturated fat, there was also a positive and significant (p<0.01) association. However, the ratio of dietary fibers, the groups of fruits and vegetables consumption was inversely associated (p<0.03). HOMA-IR values were positively associated with triglycerides, γ glutamyl transferase, hs-CRP, uric acid and systolic blood pressure. Additionally it was inversely associated with HDL-cholesterol and also with VO_2max (Figure 2).

In G3 none of the participants has reached the adequacy of dietary intake of vegetables and monounsaturated fats. There was no individual with high plasma concentrations of uric acid in G1 and G2. Participants with weight, total fat or waist circumference above normal were more likely to develop IR. The risk for IR increases

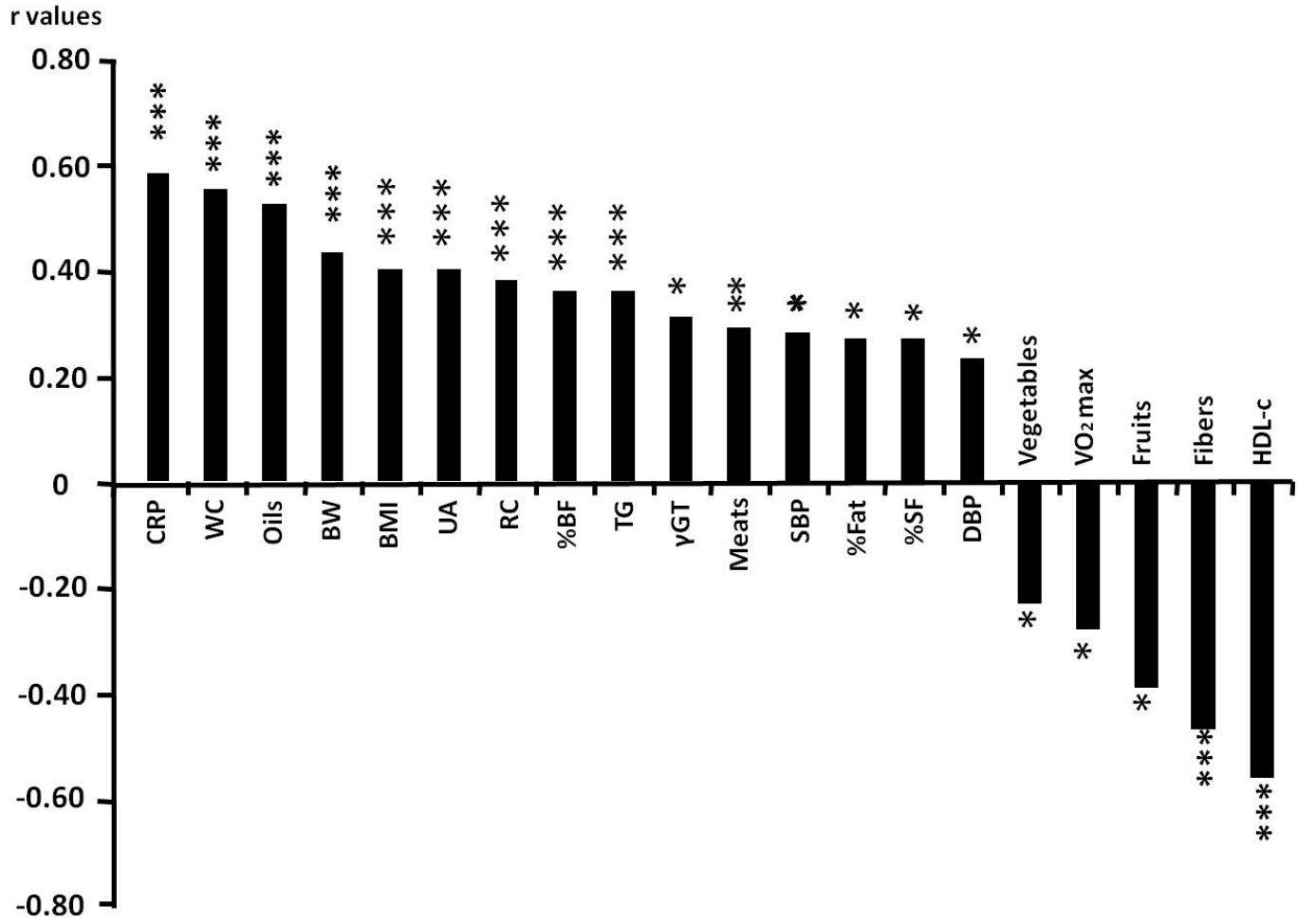

Figure 2. Relationship between HOMA-IR and clinic, dietary, anthropometric, biochemical and fitness markers.
CRP: plasma C-reactive protein; WC: waist circumference; Oils: servings of oil intaked; BW: Body Weight; BMI: body-mass index; UA: Plasma uric acid; RC: refined cereals servings; %BF: % of body fat; TG: plasma triglycerides; γGT: plasma γ glutamil transpeptidase activity; Meats: servings of meats intaked; SBP: systolic blood pressure; %Fat: % calorie as fat; %SF: % saturated fat intaked; DBP: diastolic blood pressure; VO_2max.: aerobic capacity *p<0.05, **p<0.01, ***p<0.001.

with consumption of refined grains, presence of MS, high blood pressure, triglycerides and hs-CRP concentrations (Figure 3). Some factors like adequate percentage of muscle mass, fiber intake and high levels of HDL-cholesterol played protective role for the development of IR (Figure 3).

In multiple linear regression analysis, considering log HOMA-IR as the dependent variable, was observed that IR were influenced by waist circumference, low fiber intake, high consumption of oils servings, reduced muscle mass, elevated plasma concentrations of uric acid and high BMI (Table 2).

DISCUSSION

Besides being considered an independent risk factor for cardiovascular disease, DM2 tripled the risk of death (Salles et al., 2004). According to different studies (Weickert et al., 2006; Solomon et al., 2009; Naples et al., 2010; Belalcazar et al., 2010) increased concentrations of glucose is associated with inadequate food, sedentary lifestyle, changes in body composition and biochemical variables.

In our study we observed that the indicators of excess body fat were positively associated with IR. Berggren et al. (2004) found that obese individuals have higher deposition of intramuscular fatty acid uptake and synthesis by the higher and lower hydrolysis of triglycerides, mechanisms involved in the IR.

Moreover, the location of fat also influences the development of IR. SILVA et al (2006) found positive correlations between waist circumference, HOMA-IR and triglycerides in women after adjustment for BMI. When the model was adjusted by VO_2max, was observed in men, correlations between waist, HOMA-IR and apolipoprotein B (ApoB) and also found correlations between waist and HOMA-IR in women (SILVA et al., 2006).

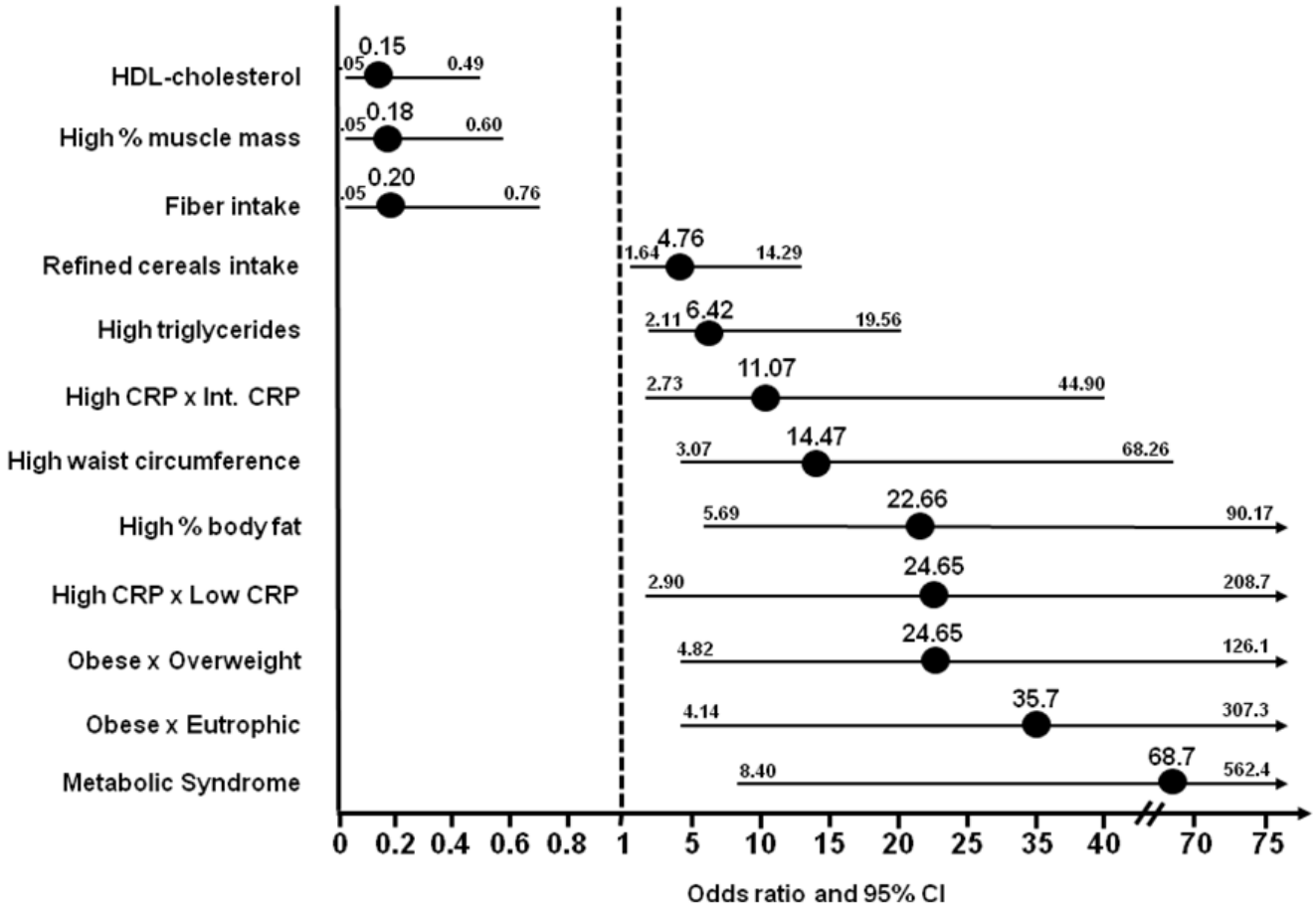

Figure 3. Odds ratios and 95% confidence intervals of insulin resistance (P75 of HOMA-IR) with variables studied. Int. CRP: intermediate concentrations of C reactive protein; $p<0.05$ for all variables.

Table 2. Multiple linear regression analysis equations for the main determinants of insulin resistance.

Predictors variable	B	P	IC (β, 95%)	
Waist circumference	0.011	0.001	0.005	0.017
Fiber intake	-0.009	0.000	-0.013	-0.005
Servings of oil intake	0.038	0.006	0.011	0.065
% Muscle mass	-0.016	0.000	-0.023	-0.009
Plasma uric acid	0.043	0.001	0.019	0.068
BMI	0.019	0.021	0.034	0.003

Adjusted R^2= 76.1%. $p<0.001$.

Another important finding is that muscle mass was associated inversely with the IR. The proposed mechanism is that the decrease in muscle mass leads to a reduction in the ability to promote oxidation of glucose and fatty acids, increasing their plasma and tissue concentrations, making a vicious cycle by increasing oxidative stress and inflammation that causes muscle tissue damage (Roubenoff, 2003; Evans et al., 2010). According to Cesari et al. (2005), sarcopenia (reduced muscle mass and strength) is associated with decreased basal metabolic rate and consequently development of non-transmissible chronic diseases such as hypertension and diabetes.

The consumption of refined foods and of fats (especially saturated fat) was associated with IR. Instead, the dietary fiber intake was considered protective factor. Some studies have shown that increased dietary fiber intake is associated with weight reduction, consequent improvement in IR and the concentrations of inflammatory and oxidative markers (Vrolix and Mensink,

2010; Domínguez et al., 2010).

According to Vrolix and Mensink (2010), low intake of whole food and high fat intake are positively associated with the development of MS. The combination of high consumption of fruits and vegetables with low consumption of saturated fatty acid is more protective against coronary artery disease (Tucker et al., 2005).

The lipid pattern showed by the IR group in this study is atherogenic, with decreased concentrations of HDL-cholesterol and high triacylglycerol. Such changes were also described by Laakso (2009) and referred to as diabetic dyslipidemia associated with the development of atherosclerosis and coronary artery disease.

We also observed that the oxidative stress and inflamematory process correlates linearly with IR. Oxidative stress in IR is well described, the main factors in promoting oxidation excess determines the state of hyperglycemia and is associated with dyslipidemia (Mota et al., 2009; Hsueh et al., 2010).

In relation to inflammatory stress, studies showed the important role of toll-like receptors (TLRs) 2 and 4 in the development of this state and consequently of DM2 (Dasu et al., 2010; Kim and Sears, 2010). Toll-like receptors are a class of cell membrane protein receptor to specifically detect pathogen-associated microbial patterns (PAMPs) during inflammatory process. Recent studies show that TLR-2 and TLR-4 can both be stimulated by lipopolysaccharide, oxidized LDL-cholesterol, heat shock protein 60, the excess of free fatty acids (FFA) and reactive oxygen species. It is known that individuals with obesity, IR and MS have elevated concentrations of FFA and thus, oxidative stress (Asehnoune et al., 2004; Song et al., 2006).

Kahn et al. (2006) showed that obesity is a major determinant of the positive association between C-reactive protein and MS in patients with diabetes. In this study it was found that the increasing in the weight influences the inflammatory stress, and those with HOMA-IR above the median (> 1.58) had ultra-sensitive C-reactive protein concentrations higher than in those with HOMA <1.58. The same was observed when analyzing the uric acid levels. In relation to homocysteine, their concentrations varied with increased BMI, regardless of the presence of a higher rate of IR.

The γ-glutamyl transferase levels were positively correlated with HOMA-IR. In addition, individuals with high enzyme activity had higher chances of developing IR. Higher activity of γ-glutamyl transferase is an independent risk factor for the development of IR (Ortega et al., 2006).

In this study, hypertension was considered an isolated risk factor. Results of "The Insulin Resistance Atherosclerosis Study" (Saad et al., 2004) showed that the IR, not insulinemia, is associated with hypertension and blood pressure in people without diabetes, with differences among ethnicities. However, in patients with DM2 the association of blood pressure and IR and insulinemia was not observed.

The cardio-respiratory fitness and muscle strength were inversely associated with IR. Some studies have documented that individuals with higher fitness reveal less risk to develop DM2 (Solomon et al., 2009; Horton, 2009). Additionally it was observed that the greater the muscle strength, the lower the incidence of MS.

In the present study we could see that the main determinants of IR are preventable factors. Moreover, the determinant variables of IR are also interconnected by acting as a cause or consequence of one another. The abdominal adiposity, a key factor for the diagnosis of both MS and excess body weight, is associated with low fiber intake and higher fat consumption. The superposition of these variables contributes to increased oxidative stress and inflammation that contribute to aggression to muscle tissue, as previously mentioned.

A vulnerability of this study is the sample size. However, it is justified by the number of variables, combined with the complexity and time taken for obtaining and analyzing data. In statistical analysis, the adjusted model was able to explain 76.1% of the variability of the sample and through a diagnostic analysis did not find points that would influence the precision of parameter estimation and the accuracy of the predicted values of the model.

The identification of the determinants of IR can lead us to develop an accurate protocol for lifestyle change, allowing the elaboration of more effective strategies.

ACKNOWLEDGMENTS

We thank Dr. Monica E. A. Inoue for contributing to the review language in this manuscript. This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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