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Original Article

Adiponectin and waist circumference as predictors of insulin-resistance in women

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SUMMARY

Background and aims: The initial disturbance of insulin resistance seems to focus on adipose tissue is a dynamic organ involved in many physiological and metabolic processes. Expresses and secretes a variety of active peptides, adipocytokines. To evaluate the prevalence of insulin-resistance in an healthy urban middle age population and to explore the role of adiponectin, inflammatory biomarkers (hs-CRP) and traditional cardiovascular risk factors as predictors of the insulin-resistance state.
Materials and methods: We studied of 176 participants (117 women and 59 men, 25–74 years), individuals with diabetes, hypothyroidism or hyperthyroidism, infectious disease, renal, or hepatic neoplasms and pregnant women were excluded. We evaluated glucose, insulin, adiponectin and hs-CRP.
Results: We found that 17.2% of individuals presented insulin-resistance. Correlation was found between waist circumference, body mass index, blood pressure and HOMA index ($p < 0.01$). Adiponectin was associated with the insulin-resistance ($p < 0.001$) but not hs-CRP. Adiponectin ($\beta = 0.385$, $p = 0.004$) and waist circumference ($\beta = 0.116$, $p = 0.02$) were predictors of IR only in women, meanwhile none of the analyzed biomarkers predicted insulin-resistance in men. Besides, postmenopausal women presented higher adiponectin levels than premenopausal 7.63 (4.46–9.58) *vs* 5.50 (3.83–7.40) μg/ml, $p = 0.01$.
Conclusions: Adiponectin and waist circumference are important predictors of insulin-resistance even in healthy non-diabetic women, they may open a new opportunity to improve current risk estimation.

1. Introduction

Cardiovascular disease represents the first leading cause of death in the world in men and women [1]; nowadays it is well known that obesity and chronic low grade inflammatory state are associated with the presence of cardiovascular disease [2,3].

Obesity is the most prevalent nutrition-related disorder in Western countries, and the prevalence of overweight and obesity is increasing worldwide at an alarming rate [3] being both, developed and developing countries, affected as well. The health consequences of obesity are many and varied, ranging from an increased risk of premature death to several non-fatal diseases but with adverse impact on quality of life.

Although increased body mass index (BMI) is a powerful predictor of metabolic disease risk, individuals with the same BMI may have greatly different amounts of visceral (central or abdominal) fat associated with the greatest metabolic risk [4,5].

The current view of adipose tissue is that of an active secretory organ sending out and responding to signals that modulate appetite, insulin sensitivity, energy expenditure, inflammation, and immunity. The association between accumulation of visceral adipose tissue and insulin resistance (IR) is well established in obesity and type 2 diabetes [6,7].

Abdominal obesity, when accompanied by metabolic derangements, including IR, low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides (TG) and raised blood pressure, increases significantly the predicted cardiovascular disease risk and constitutes the well known metabolic syndrome [4,8].

Abdominal fat deposition is different according to gender, being more common in men than in young women [9]; however, redistribution of fat accumulation from peripheral locations toward increased intra-abdominal depots, is common after the menopause [10,11].

Adiponectin, derived mainly from adipose tissue, is considered an insulin sensitizer and it upholds both anti-atherogenic and anti-inflammatory effects [12–16].

Although generally circulating at high concentrations in human plasma, adiponectin was found reduced in obese, IR and diabetes in animals and humans [12,14,15] and has been regarded as a

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potential link between adiposity and increased cardiovascular risk in these patients [13].

However, it is still unclear whether the decrease in adiponectin is cause or consequence of the IR state. Nevertheless, according to prospective studies and associated meta-analysis, any association between adiponectin levels and future CHD is unlikely to be strong [17]. Also, several other published studies on the prospective association between adiponectin and CVD have shown inconsistent results [18–20]. Some of these controversies may be due to the different behavior of adiponectin in women and men. Women have higher serum concentrations of adiponectin than men nevertheless large differences exist between genders with regard to apparent adiponectin sensitivity [21].

Our aim was to assess the prevalence of IR in a middle age urban population of men and women, and to explore the role of adiponectin, inflammatory biomarkers (hs-CRP) and traditional cardiovascular risk factors as predictors of the IR state.

2. Materials and methods

2.1. Subjects

The present study is part of a preventative case-finding program developed since 2001 in the city of Posadas, Argentina. This program included 1000 public employees from 2 national Hospitals (Dr. Ramón Madariaga and Dr. Fernando Barreyro hospitals) [22]. The intention was to screen large strata of the adult population every two years, to identify high-risk individuals for preventative interventions. Subjects were invited to participate in health screening, including physical examination, laboratory tests and a standardized questionnaire on medical and medication history, smoking status (current *vs* previous or never), alcohol consumption, physical activity, and women's menopausal status. A total of 1000 participants were evaluated between 2001 and 2011. For the present study, a subsample of 176 participants (117 women and 59 men, 25–74 years) was evaluated between 2011 and 2012. The exclusion criteria included diabetes, hypo and hyperthyroidism, chronic renal disease, hepatic or infectious diseases and cancer, pregnant women were also excluded. None of the women were under hormone replacement therapy. All participants gave their written informed consent and the original screening study protocol was approved by the Ethics Committee of the hospitals.

Anthropometrics measurements such as height, weight, and waist circumference were taken. Waist circumference was measured around the abdomen just above the hip bone, cut off values were considered according to the Adult Treatment Panel III [23]. Body mass index was calculated from the ratio of body weight in kilograms (kg) to height in square meters and expressed as kg/m^2 units. Participants were classified as normal weight, overweight or obese, according to WHO classification [24].

Blood pressure (BP) was measured according to the American Heart Association [25] twice, with a mercury sphyngomanometer, after weight and height measurements. Subjects seated in a separate and quiet room for 15 min with their back supported and feet on the ground. Two BP readings were taken at a 5-min interval. The mean of the two measures was used. Participants were classified as normotensive (BP $<$ 120/80 mmHg), pre-hypertensive (BP $\geq$ 120/80 mmHg and $<$140/90 mmHg) and hypertensive (BP $\geq$ 140/90 mmHg or under antihypertensive treatment).

2.2. Sample collections

Blood samples were obtained by venipuncture after a requested 12-h fast. The serum was separated by centrifugation within an hour after collection and distributed to aliquots. The aliquots for the assessment of insulin, adiponectin and hs-CRP were frozen at −80 °C until the assay was performed.

2.3. Analytical methods

The measurement of glucose, total-cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides (TG) was performed within 24 h of collection using a fully automated analyzer Dimension RxL Max Clinical Chemistry System (Siemmens). The intra-assay (CVi) and inter-assay (CVe) variation coefficients for TG were 2.45% and 1.74%, 3.41% and 2.6% for HDL-chol, and 2.41% and 2.2% for glucose, respectively. We also calculated the ratio of TG/HDL-chol, which is considered a surrogate marker of insulin resistance [26].

Hs-CRP and insulin were determined by a chemoluminiscent method (Immulite autoanalyzer, Siemens, LA, USA). The CVi and CVe for hs-CRP were 2.10% and 2.0%, and for insulin 4.20% and 3.50%, respectively. The surrogate marker of insulin resistance, Homeostasis Model Assessment (HOMA) index, was calculated as: fasting serum insulin (U/mL) $\times$ fasting serum glucose (mmol/L)/22.5 [27]. According to our previous studies, we considered IR those participants with an HOMA index $\geq$ 2.6 [22].

Plasma adiponectin (mg/L) was determined using a commercial available ELISA kits (SEACP S.R.L. – Florence, Italy) with monoclonal antibodies (ALPCO immunoassays). The sensitivity of the assay was 0.17 ng/ml. The CVi was 3.20% and the CVe was 3.05%.

2.4. Statistical analysis

Data are as mean presented ± SD or median (range) according to normal or skewed distribution, evaluated through Kolmogorov–Smirnov test. Differences between groups were tested using the unpaired Student t test, χ^2 test, or the Mann–Whitney U test, according to the data distribution. Pearson or Spearman analysis, for parametric or nonparametric variables, was used to determine correlations between parameters. Stepwise and multiple linear regression analyses were used to indentify independent correlates of IR and different variables. Previously, each variable was examined for normal distribution, and abnormally distributed variables were log-transformed. The SPSS 19.0 software package (Chicago, IL) was used for statistical analysis. A $p < 0.05$ was considered significant.

3. Results

Details about the studied cohort are given in Table 1. According to BMI, 24.3% were normal weight, 38.6% presented overweight and 37.3% were obese. Waist circumference was increased in 44.6% of the participants, this percentage was higher in women (55%)

Table 1
Clinical and epidemiologic characteristics of study population (n = 176).

Variables	Mean ± SD
Age (years)	49.0 ± 9.3
Waist circumference (cm)	
Female	90.3 ± 13.2
Male	96.8 ± 10.3
Body mass index (kg/m^2)	28.8 ± 5.5
Systolic blood pressure (mmHg)	126.6 ± 18.0
Diastolic blood pressure (mmHg)	84.6 ± 12.5
Variables	**Medians (25th–75th)**
Fasting blood glucose (g/l)	0.82 (0.73–0.90)
Fasting blood insulin (μU/ml)	4.0 (2.0–8.4)
HOMA	0.81 (0.43–1.84)
TG/HDL-chol index	2.46 (1.51–3.77)
Adiponectin (μg/ml)	5.47 (3.82–7.96)
Hs-CRP (mg/l)	2.40 (3.82–7.96)

25th: percentile 25; 75th: percentile 75. Data are expressed as mean ± SD or median (range) according to data distribution.

Table 2
Anthropometric and biochemical characteristics of the study population divided according to insulin-resistant state (n=176).

Variables	IS	IR	*p-value*
Age (years)	48.8 ± 9.6	49.9 ± 7.8	NS
Body mass index (kg/m^2)	27.8 ± 4.8	33.6 ± 6.0	<0.001
Waist circumference (cm)			
Female	87.3 ± 11.6	102.9 ± 11.7	<0.001
Male	95.5 ± 9.6	105.6 ± 10.8	0.014
Systolic blood pressure (mmHg)	124.8 ± 17.2	135.4 ± 19.2	0.003
Diastolic blood pressure (mmHg)	83.0 ± 11.5	91.9 ± 14.4	<0.001
Fasting blood glucose[a] (g/l)	0.81 (0.73–0.88)	0.89 (0.82–1.0)	0.001
Adiponectin[a] (μg/ml)	5.87 (4.03–8.50)	4.15 (2.18–5.97)	<0.001
Hs-CRP[a] (mg/l)	2.20 (0.80–4.70)	3.30 (2.20–5.70)	0.028
TG/ HDL-chol index[a]	2.10 (1.45–3.51)	3.42 (2.46–4.84)	0.002

25th: percentile 25; 75th: percentile 75. Data are expressed as mean ± SD or median (range).
[a] Mann Withney *U* test – Student' test according to data distribution; IS: insulin-sensitive. IR: insulin-resistant

Table 3
Insulin resistance and its relation to plasma concentrations of adiponectin and hs-CRP in the study population divided by gender and IR state (n = 176).

Variables	Median (25th–75th)	Mann Withney *U* test	*P*
Adiponectin (μg/ml)			
Female			
IS	6.97 (4.77–9.21)	472	<0.001
IR	4.30 (2.66–6.09)		
Male			
IS	4.24 (3.12–5.89)	97	NS
IR	2.48 (1.80–4.68)		
Hs-CRP (mg/l)			
Female			
IS	2.40 (1.0–4.80)	674	0.018
IR	4.50 (2.27–6.55)		
Male			
IS	1.20 (0.70–3.0)	160	NS
IR	2.50 (0.80–3.80)		

25th: percentile 25; 75th: percentile 75. Data are expressed as median (range) Mann Withney *U* test; *P*: *p*-value; IS: insulin-sensible. IR: insulin-resistant

than in men (25%), $p < 0.001$. Regarding BP, 26.6% of the participants were pre-hypertensive and 50.6% presented hypertension or were under anti-hypertensive treatment.

Regarding IR markers, HOMA index correlated with BMI ($r = 0.54$, $p < 0.001$), waist circumference ($r = 0.61$, $p < 0.001$), systolic and diastolic blood pressure ($r = 0.31$ and $r = 0.35$, $p < 0.007$) and with the TG/HDL-chol index ($r = 0.35$, $p < 0.001$).

Adiponectin was below the reference value in 45.7% of the participants, being lower in men 4.23 μg/ml (3.90–5.22) than in women 6.23 μg/ml (6.20–7.34) $p < 0.001$. As expected, adiponectin levels inversely correlated with BMI ($r = 0.24$, $p < 0.021$) and HDL-chol ($r = 0.39$, $p < 0.001$). Also inverse correlations were observed between adiponectin and HOMA index ($r = 0.29$, $p < 0.001$) and TG/HDL-chol index ($r = 0.45$, $p < 0.001$). Interestingly, only inverse correlation between adiponectin and waist circumference was observed in women ($r = 0.19$, $p = 0.04$) but not in men.

Hs-CRP was higher than the cut-off value of high risk (3.0 mg/l) in 41.2% of the participants.

When participants were divided according to the HOMA index in IR (≥2.6) and insulin sensible (IS < 2.6), we observed that 17.2% ($n = 31$) of the participants presented IR. Adiponectin was lower in the IR group; meanwhile BMI, waist circumference, blood pressure, hs-CRP and TG/HDL-chol were higher (Table 2). Although the percentage of men with IR was lower than women (12.5% *vs* 20%), the difference was not statistically significant.

Table 3 shows adiponectin and hs-CPR concentrations in IR and IS participants divided by gender. Women presented higher values of hs-CRP and adiponectin that men, in IR either IS group.

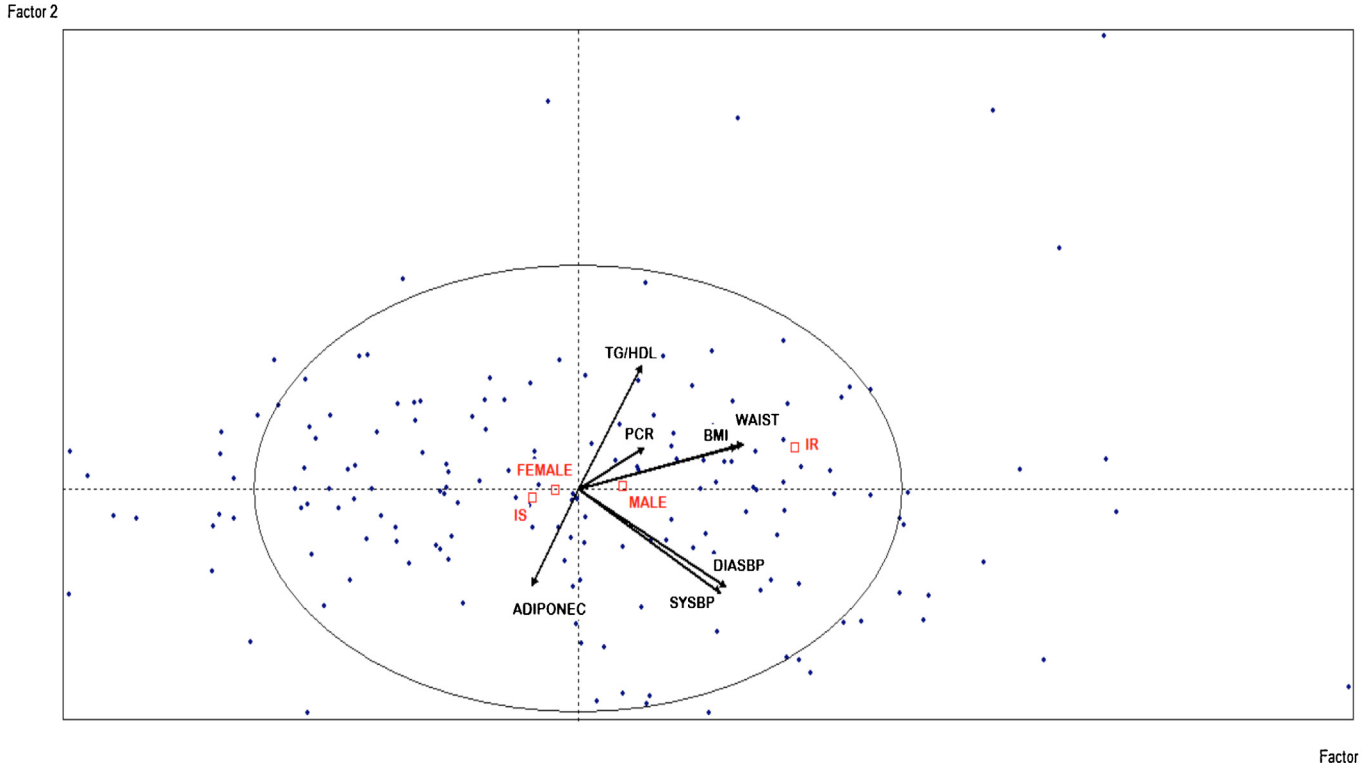

Fig. 1. Multivariate analysis of main components. Study variables analyzed and pressure; DIASBP: diastolic blood pressure; PCR: high sensitive protein c reactive.

Table 4
Adiponectin concentrations in pre and postmenopausal women.

Variables	Premenopausal ($n = 46$)	Posmenopausal ($n = 71$)	Mann Withney U test	P
Age (years)[a]	39 ± 5	55 ± 5		
Adiponectin (μg/ml)	5.50 (3.83–7.40)	7.63 (4.46–9.58)	1171.50	0.010

[a] Data are expressed as mean ± SD or median (range) according to data distribution.

The multivariate analysis including the studied variables showed that BMI, waist circumference, blood pressure, hs-CRP and TG/HDL-chol index and male gender represented the IR state with higher power. Meanwhile adiponectin and female gender were representative of IS state (Fig. 1).

After logistic regression analysis, adiponectin ($\beta = 3.68$, $p < 0.001$), waist circumference ($\beta = 0.113$, $p = 0.016$) and gender ($\beta = 2.08$, $p = 0.007$) were the most important predictors of IR in the whole population. When the same analysis was performed in the population divided by gender, only in women adiponectin ($\beta = 0.385$, $p = 0.004$) and waist circumference ($\beta = 0.116$, $p = 0.02$) were predictors of IR, meanwhile none of the analyzed biomarkers predicted IR in men.

Given the middle age of the studied women, and the number of postmenopausal women, we evaluated the impact of menopausal status on adiponectin levels. Postmenopausal women presented higher adiponectin levels than premenopausal 7.63 (4.46–9.58) *vs* 5.50 (3.83–7.40) μg/ml, $p = 0.01$ (Table 4).

4. Discussion

In our study population we observed that the incidence of IR was 17.2%, without differences between men and women. However, adiponectin and female gender was representative of insulin-sensitivity; meanwhile BMI, waist circumference, BP, hs-CRP and male gender represented the IR state with higher power. Besides, postmenopausal women presented higher values of adiponectin than premenopausal.

We found lower values of IR and obesity (37.3%) than the published by other authors, who relate IR frequencies ranging from 25% to 39.6% and obesity from 50% to 60% [28–30]. The differences are probably due to the severe exclusion criteria used in this study, such as diabetes; meanwhile, most of the published studies include general population. Nevertheless, in our study positive correlations were found between IR markers and general and abdominal obesity. Obesity is considered one of the main factors in the etiology of IR as was shown in many epidemiological studies [4,7,9,14,15]. The highly significant correlation found in this study between the waist circumference and HOMA index in healthy population, is a valuable element for supporting that central fat accumulation as one of the primary alterations that trigger the sequence of events that promotes IR.

Various mechanisms have been identified that relate the adipose tissue with a reduced response to the actions of insulin [5,9,15,30,31]. Furthermore, in this study serum adiponectin concentration was significantly associated with IR and after dividing the population in IR and IS, IR individuals presented lower adiponectin levels. Many *in vivo* and *in vitro* studies, both in animals and humans have reported the existence of strong negative correlations between adiponectin and IR [14–16,20]. It remains unclear whether low adiponectin levels are the cause or the consequence of these conditions. It is interesting to speculate that variations in ADIPOQ gen may decrease the circulating hormone levels, and thus predispose to IR, but it has also been observed that once the IR is developed, circulating levels of adiponectin are reduced, and this could be due to the existence of genetic susceptibility to IR conferred by ADIPOQ gene polymorphisms [32,33]. Although more studies to clarify these controversies are necessary, the evidence to date warns that the decline of this hormone in the IR is frequent [34].

Several studies have shown that serum levels of hs-CRP correlate with future risk of cardiovascular events since an inflammatory component has been well recognized in the atherosclerosis process and IR [35,36]. In the present study, hs-CRP circulating levels were significantly higher than the cut off risk value in nearly half of the participants, and the IR group presented increased values compared with IS group, being higher in women than men. Although negative correlations between plasma hs-CRP levels and adiponectin have been previously reported [37], we did not find any correlation between adiponectin and hs-CRP circulating levels, like others [37]. The lack of association suggests that the systemic inflammation as part of the relationship of adiponectin with obesity or atherosclerosis is multifactorial depending on many other contributed mediators.

When we analyzed the figure with the seven main variables considered, the first factorial plane that presented the highest representativeness of the IR state included the increase in the variables TG/HDL-chol, general and abdominal obesity, high hs-CRP and decreased adiponectin concentrations. In addition female gender was directly related to IS state. Because gender was a factor that explained the IR independently, we assessed whether the behavior was similar in both men and women, from the analysis emerged that only in female gender adiponectin concentration and abdominal obesity are predictors of IR. Moreover, recently it has been proposed that examining adiponectin level in conjunction with abdominal fat could improved the ability to detect metabolic syndrome, especially in women [37].

The behavior of adiponectin in men and women has been previously studied [38] presenting women higher values than men. It has been reported that adiponectin level in postmenopausal women was higher than that in premenopausal women after adjustment for age, fat mass and fat distribution [39]. However, Sieminska et al. reported that serum adiponectin level was not influenced by menopausal status [39,40]. In the present study we observed higher adiponectin levels in postmenopausal women, in accordance to Matsui [39]. It has been demonstrated that adiponectin levels were increased with age in men and women [39,41]. In turn, Matsui et al. [39] have suggested that the effect of endogenous androgen on the change in adiponectin may be superior to that of endogenous estrogens in women.

Our study has some limitations; first, this study was a cross-sectional design, which does not allow us to make causal inferences between adiponectin and other hormones; in addition, changes in hormones may not be uniform because our study included women with different sex hormone levels; although the number of the study population is interesting, it does not allow us to perform epidemiological conclusions.

Finally, in our study population one of five individuals presented IR. The best parameters that explained the IR event were abdominal obesity and adiponectin concentration but only in women.

Conflict of interest statement

The authors hereby declare that no conflict of interest exists with regard to any material described in this work.

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