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Original Article

High waist-to-hip ratio levels are associated with insulin resistance markers in normal-weight women

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ABSTRACT

Aim: To assess the association between high waist-to-hip ratio (WHR) levels and insulin resistance (IR) or hyperinsulinemia after oral glucose tolerance test (OGTT) in a sample of normal-weight women.
Methods: We conducted an analytical cross-sectional study in euthyroid non-diabetic women, who attended the outpatient service of a private clinic in Lima-Peru from 2012 to 2016. Participants were divided in two groups according to the presence or absence of high WHR levels, IR or hyperinsulinemia after OGTT. We considered WHR values > 0.85 as high levels. IR was defined as a Homeostasis Model Assessment (HOMA-IR) value > 2.39 and hyperinsulinemia after OGTT as a serum insulin value ≥ 80μU/mL after 120 min of 75-g glucose intake. We elaborated crude and adjusted Poisson generalized linear models to evaluate the association between high WHR levels and IR or hyperinsulinemia after OGTT and reported the prevalence ratio (PR) with their respective 95% confidence intervals (95%CI).
Results: We analyzed the data of 248 euthyroid, non-diabetic and normal-weight women. The prevalence of high WHR levels was 68.9% (n = 171) while the prevalence of IR and hyperinsulinemia after OGTT was 25% (n = 62) and 15.3% (n = 38), respectively. WHR values were positively correlated with HOMA-IR (r = 0.307; p < 0.001) and serum insulin after OGTT (r = 0.260; p < 0.001). In the adjusted model, high WHR levels were associated with both IR (aPR = 2.63; 95%CI: 1.39–5.01) and hyperinsulinemia after OGTT (aPR = 2.35; 95%CI: 1.03–5.38).
Conclusion: High WHR levels were associated with both IR markers used in our study, appearing to be a useful anthropometric indicator to assess IR in euthyroid normal-weight women without type 2 diabetes mellitus.

1. Introduction

Insulin resistance (IR) is a metabolic condition that implies a decreased physiological response of peripheral tissues to insulin action [1,2]. IR plays a key role in the pathogenesis of cardiovascular diseases (CVDs) and is a recognized feature of disorders implicated in impaired glucose tolerance and type 2 diabetes mellitus (T2DM) [3–5].

The development of IR is closely related to obesity, especially to central obesity [6–11], since different studies have shown that visceral adipose tissue (VAT) could release inflammatory cytokines and produce oxidative stress that alters the insulin action [12,13]. In fact, recent studies have found that central obesity is associated with higher mortality than Body Mass Index (BMI)-defined obesity [14,15]. Furthermore, in recent years, it has been established that

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the presence of metabolic disorders in normal-weight individuals was not uncommon [16–23] and that visceral fat accumulation might be particularly detrimental for women [24,25].

There are several measures that have been used to assess obesity, but all have different limitations. Among them, the BMI, used for a long time as a reference to diagnose and classify obesity, does not quantify visceral fat, nor does it differentiate between excess fat, muscle, or bone mass [6,26]. Currently, there are more accurate techniques to assess VAT, such as bioimpedance [27,28] and dual-energy x-ray absorptiometry (DEXA) [29,30]; however, the availability of equipment is still limited. Thus, reliable, accessible, easy-to-measure and non-invasive alternatives are needed.

On the other hand, direct methods for measuring IR are relatively complex [31]. The hyperinsulinemic-euglycemic clamp, based on the intravenous infusion of insulin and glucose is considered the gold standard [32], but its complexity hinders its clinical use. For this reason, indirect methods have been developed, one of the most widely used is the HOMA-IR, which uses a mathematical model to calculate IR with the fasting serum insulin and fasting plasma glucose values [33,34].

Some studies have highlighted the importance of the waist-to-hip ratio (WHR) as an anthropometric indicator for both VAT [35,36] and IR [22,37]. However, only one of them was performed in normal-weight adults [22], which, as already mentioned, may also suffer from metabolic disorders [16–23].

For the above mentioned, the objective of the present study was to assess the association between high WHR levels and IR or hyperinsulinemia after oral glucose tolerance test (OGTT) in a sample of normal-weight women.

2. Methods

2.1. Study design and population

We carried out an analytical cross-sectional study in euthyroid women with a normal BMI (18.50–24.99 kg/m^2) and no medical history of T2DM, who attended the outpatient service of a private clinic in Lima-Peru, during 2012–2016.

2.2. Sample type and analysis unit

A non-probabilistic sampling was performed. The sample consisted of all women who attended the outpatient service of the private clinic between January 2012 and December 2016 and met the eligibility criteria of the study.

2.3. Procedures

We reviewed all the medical records of the patients treated during the study length and collected all the data of interest. The laboratory values were only collected if the patient laboratory tests were performed with a maximum of 30 days after they were attended. All participants had a minimum fasting period of eight hours for laboratory tests, according to the protocols established by the private clinic.

2.4. Eligibility criteria

We included women aged ≥18 with a BMI between 18.50 and 24.99 kg/m^2 and no medical background of T2DM, hypothyroidism, subclinical hypothyroidism, hyperthyroidism, polycystic ovary syndrome or metabolic syndrome. In addition, we excluded women aged ≥60, with fasting glucose values ≥ 126 mg/dL, oral glucose tolerance test (OGTT) ≥200 mg/dL, thyroid hormones values outside the following ranges: free triiodothyronine (FT3): 2.3–4.2 pg/mL, free thyroxine (FT4): 0.89–1.76 ng/dL, thyroid stimulating hormone (TSH): 0.40–5.0 μU/mL [38]; and pregnant women.

2.5. Variables definition

2.5.1. Exposure: WHR levels

The WHR was defined using the following calculation: waist circumference (in centimeters)/hip circumference (in centimeters). Besides, the women were categorized in two groups: normal WHR levels (WHR values ≤ 0.85) and high WHR levels (WHR values > 0.85) [39,40].

2.5.2. Outcomes: IR and hyperinsulinemia after OGTT

IR was defined as a HOMA-IR value ≥ 2.39, that correlates with the 75-percentile. We used this cut-off point based in a previous study [41]. Mathews et al. (1985) proposed HOMA-IR in a mathematical model to assess hyperinsulinemia. The gold standard to assess IR is the hyperinsulinemic euglycemic clamp, however HOMA-IR is well correlated with it. HOMA-IR was calculated using the formula: fasting glucose (mg/dL) x fasting insulin (μU/mL)/405 [34].

Hyperinsulinemia after OGTT was defined as a serum insulin value ≥ 80 μU/mL after 120 min of 75-g glucose intake [42]. Participants were divided in two groups according to these criteria.

2.5.3. Other variables

The following variables were also included in the analysis: age (years), BMI, fasting glucose, postprandial glucose, fasting insulin, FT3, FT4 and TSH.

2.6. Statistical analysis

We used STATA v14.0 (StataCorp, TX, USA) for our analysis. Descriptive results for numeric variables were presented as means with standard deviation (SD) or medians with interquartile range (IQR), depending on their distributions; otherwise, we expressed the qualitative variables as numbers with percentages. The study population characteristics according to the WHR levels, IR or hyperinsulinemia after OGTT were compared using the student T test or the Wilcoxon rank sum test as appropriate for continuous variables and using the Chi-square test for categorical variables.

The Pearson correlation coefficient (rho) was used to assess the relationship between numeric variables as WHR and HOMA-IR or serum insulin after OGTT values. For correlations, the numeric variables were transformed to a normal distribution using a logarithmic transformation. The correlations were graphed using scatter plots.

Two generalized linear models (1 crude and 1 adjusted) from Poisson family with robust standard errors were constructed to evaluate the association between high WHR levels and IR or hyperinsulinemia after OGTT. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95%CI). The adjusted model included the following confounding variables: age (years), FT3 (pg/mL) and TSH (μU/mL [38]; and the reported association measure was the adjusted prevalence ratio (aPR) with their respective 95%CI.

2.7. Ethical considerations

The data was collected by two researchers from the private clinic to study epidemiological surveillance. For this study, participant information was delivered in a Microsoft Excel 2010 spreadsheet without biological identifiers, maintaining the confidentiality of the data.

3. Results

In total, we enrolled 2047 patients during the study period; we excluded 185 and 50 participants because they were older than 60 or less than 18 years; respectively. Additionally, 296 patients were withdrawn due to hyperthyroidism, hypothyroidism, subclinical hypothyroidism or T2DM; 874 because their BMI was not between 18.50 and 24.99 kg/m^2, 30 because were males and 364 because they did not have the variables of interest. Finally, we analyzed 248 euthyroid, non-diabetic and normal-weight women.

3.1. Characteristics of the study population

The average age of the participants was 33.9 ± 10.6 (SD) years and the median BMI was 22.4 ± 1.7 (SD) kg/m^2. The prevalence of high WHR levels was 68.9% (n = 171) while the prevalence of IR and hyperinsulinemia after OGTT was 25% (n = 62) and 15.3% (n = 38) respectively (Table 1).

The FT3, FT4, and TSH, mean or median levels were 3.1 ± 0.4 (SD) pg/mL, 1.2 ± 0.2 (SD) ng/dL and 2.3 (IQR: 1.4–3.1) μU/mL, respectively. Furthermore, the fasting glucose, fasting insulin and HOMA-IR, mean or median levels were 85.8 ± 7.8 (SD) mg/dL, 7.7 (IQR 5.7–10.9) (μU/mL) and 1.6 (IQR: 1.1–2.4), respectively. The group with normal WHR levels had a mean of 0.83 ± 0.02 (SD), while the high WHR levels group had a mean of 0.88 ± 0.02 (SD), with statistically significant differences (Table 1).

3.2. Characteristics of the study population by WHR levels

We found higher means or medians of BMI (23.1 vs. 20.7; p < 0.001), fasting insulin (8.5 vs. 6.2; p < 0.001), serum insulin after OGTT (42.2 vs. 33.2; p < 0.001) and HOMA-IR (1.8 vs. 1.3; p < 0.001) in participants with high WHR levels compared with the normal WHR levels group (Table 1).

3.3. Characteristics of the study population based on IR

The prevalence of IR was higher in the group with high WHR levels (30.9 vs 11.6%; p < 0.001). We found higher means of WHR (0.88 vs 0.86; p < 0.001), BMI (23.0 vs. 22.1; p < 0.001), fasting glucose (91.5 vs. 83.9; p < 0.001), postprandial glucose (106.9 vs. 88.4; p < 0.001), FT3 (3.2 vs. 3.1; p = 0.026) in participants with IR compared with the no IR group. Equally, we observed higher medians of fasting insulin (13.6 vs. 6.7; p < 0.001), serum insulin after OGTT (75.2 vs. 34.2; p < 0.001) and HOMA-IR (3.1 vs. 1.4; p < 0.001) in participants with IR compared with the no IR group (Table 2).

3.4. Characteristics of the study population based on hyperinsulinemia after OGTT

The prevalence of hyperinsulinemia after OGTT was higher in the group with high levels of WHR (18.7% vs 7.8%; p < 0.001). We found a higher mean of WHR (0.88 vs 0.86; p < 0.001), fasting glucose (89.4 vs. 85.1; p < 0.001), postprandial glucose (116.8 vs. 88.7; p < 0.001), FT3 (3.2 vs. 3.1; p < 0.001) in participants with hyperinsulinemia after OGTT compared with the normal group. Furthermore, we observed higher medians of fasting insulin (12.9 vs. 7.1; p < 0.001), serum insulin after OGTT (111.9 vs. 35.3; p < 0.001) and HOMA-IR (3.0 vs. 1.5; p < 0.001) in participants with hyperinsulinemia after OGTT compared with the group without this condition (Table 3).

3.5. Correlations between the WHR values and the logarithmic HOMA-IR or serum insulin after OGTT values

We found a positive correlation between the WHR values and the logarithmic HOMA-IR values (r = 0.307; p < 0.001) (Fig. 1). In the same way, we found a positive correlation between the WHR values and the logarithmic values of serum insulin after OGTT (r = 0.260; p < 0.001) (Fig. 2).

3.6. Generalized linear models from Poisson family to assess the association between high WHR levels and IR or hyperinsulinemia after OGTT

In the crude Poisson regression model to evaluate the association between high WHR levels and IR, compared with the normal WHR levels group, the prevalence of IR was higher (PR = 2.65; 95% CI: 1.34–5.10). Similarly, the association remained in the adjusted model for age (years), FT3 (pg/mL) and TSH (μU/mL) (aPR = 2.63; 95%CI: 1.39–5.01) (Table 4).

In the crude Poisson regression model to assess the association between high WHR levels and hyperinsulinemia after OGTT, compared with the normal WHR levels group, the prevalence of hyperinsulinemia after OGTT was higher (PR = 2.40; 95%CI: 1.05–5.51). Finally, after adjusting for age (years), sex, FT3 (pg/mL) and TSH (μU/mL), the association remained statistically significant (aPR = 2.35; 95%CI: 1.03–5.38) (Table 4).

4. Discussion

4.1. Main findings

To our knowledge, this is one of the first studies that assessed the association between WHR and IR in normal-weight women.

Table 1
Characteristics of the study population by WHR levels (N = 248).

Variables	N = 248	Normal (n = 77)	High (n = 171)	P value
Age (years)	33.9 ± 10.6	34.6 ± 8.2	40.2 ± 11.4	0.107
BMI (kg/m^2)	22.4 ± 1.7	20.7 ± 1.3	23.1 ± 1.3	<0.001
WHR	0.87 ± 0.03	0.83 ± 0.02	0.88 ± 0.02	<0.001
Fasting glucose (mg/dL)	85.8 ± 7.8	84.7 ± 6.6	86.3 ± 8.3	0.125
Postprandial glucose (mg/dL)	93.0 ± 22.4	88.3 ± 19.8	95.2 ± 23.2	0.026
Fasting insulin (μU/mL)	7.7 (5.7–10.9)	6.2 (4.9–8.7)	8.5 (6.2–11.9)	<0.001
Serum insulin after OGTT (μU/mL)	40.1 (25.7–65.9)	33.2 (20.1–49.9)	42.2 (29.1–70.9)	<0.001
HOMA-IR	1.6 (1.1–2.4)	1.3 (1.1–1.8)	1.8 (1.3–2.6)	<0.001
FT3 (pg/mL)	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	0.720
FT4 (ng/dL)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.1	0.496
TSH (μU/mL)	2.3 (1.4–3.1)	2.2 (1.4–3.1)	2.4 (1.6–3.6)	0.669

Data expressed as mean ± standard deviation, median (interquartile range).

Table 2
Characteristics of the study population based on IR (N = 248).

Variables	No IR (n = 186)	IR (n = 62)	P value
High WHR levels	118 (69.1)	53 (30.9)	0.001
Age (years)	34.1 ± 10.2	33.3 ± 11.7	0.600
BMI (kg/m^2)	22.1 ± 1.7	23.0 ± 1.6	<0.001
WHR	0.86 ± 0.03	0.88 ± 0.03	<0.001
Fasting glucose (mg/dL)	83.9 ± 6.1	91.5 ± 9.4	<0.001
Postprandial glucose (mg/dL)	88.4 ± 19.3	106.9 ± 25.4	<0.001
Fasting insulin (μU/mL)	6.7 (4.9–8.3)	13.6 (11.9–16.7)	<0.001
Serum insulin after OGTT (μU/mL)	34.2 (22.5–49.3)	75.2 (51.3–109.7)	<0.001
HOMA-IR	1.4 (1.1–1.7)	3.1 (2.7–3.8)	<0.001
FT3 (pg/mL)	3.1 ± 0.4	3.2 ± 0.4	0.026
FT4 (ng/dL)	1.2 ± 0.2	1.1 ± 0.1	0.007
TSH (μU/mL)	2.3 (1.4–3.2)	2.3 (1.6–2.8)	0.789

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

Table 3
Characteristics of the study population based on hyperinsulinemia after OGTT (N = 248).

Variables	No hyperinsulinemia after OGTT (n = 210)	Hyperinsulinemia after OGTT (n = 38)	P value
High WHR levels	139 (81.3)	32 (18.7)	0.027
Age (years)	33.9 ± 10.3	33.7 ± 12.2	0.934
BMI (kg/m^2)	22.2 ± 1.7	22.3 ± 1.6	0.011
WHR	0.86 ± 0.03	0.88 ± 0.03	<0.001
Fasting glucose (mg/dL)	85.1 ± 7.3	89.4 ± 9.7	<0.001
Postprandial glucose (mg/dL)	88.7 ± 19.6	116.8 ± 22.5	<0.001
Fasting insulin (μU/mL)	7.1 (5.1–9.9)	12.9 (9.5–18.2)	<0.001
Serum insulin after OGTT (μU/mL)	35.3 (23.6–50.4)	111.9 (97.4–138.1)	<0.001
HOMA-IR	1.5 (1.1–2.1)	3.0 (2.0–4.2)	<0.001
FT3 (pg/mL)	3.1 ± 0.4	3.2 ± 0.4	0.017
FT4 (ng/dL)	1.2 ± 0.2	1.1 ± 0.1	0.002
TSH (μU/mL)	2.3 (1.5–3.5)	2.5 (1.9–3.8)	0.060

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

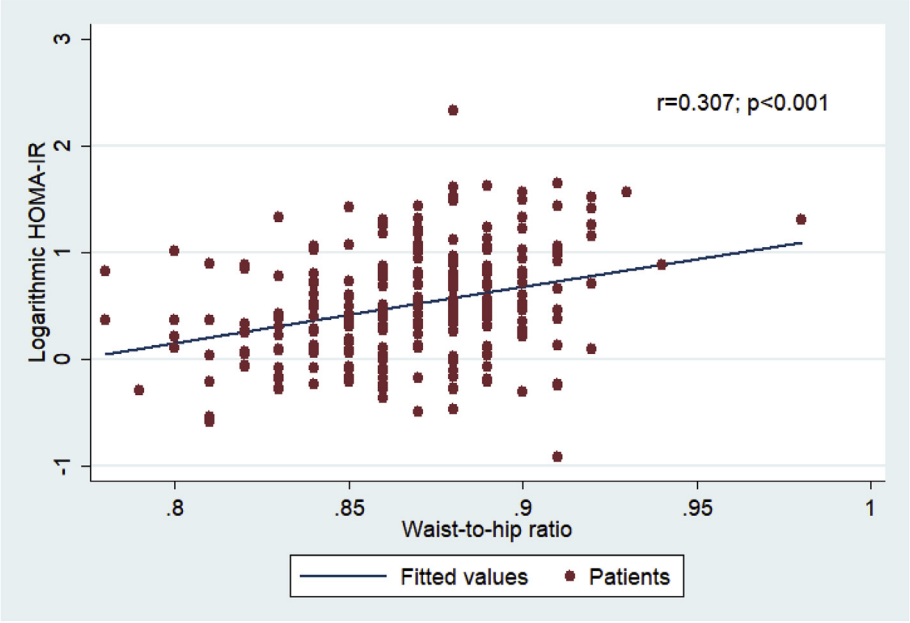

Fig. 1. Scatter plot for the correlation between the WHR values and the logarithmic HOMA-IR values.

We found that WHR was positively correlated with the HOMA-IR and serum insulin after OGTT values. Similarly, we found that the high WHR was associated with both IR and hyperinsulinemia after OGTT.

4.2. Comparison with other studies

Previous studies have highlighted the importance of the WHR as an anthropometric indicator for both VAT [35,36] and IR [22,37].

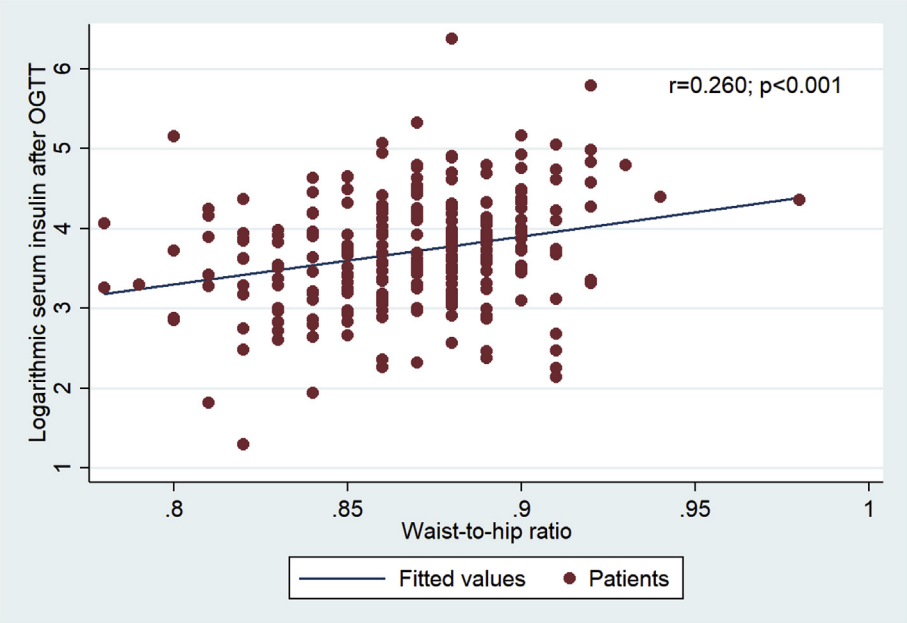

Fig. 2. Scatter plot for the correlation between the WHR values and the logarithmic serum insulin after OGTT values.

Table 4
Generalized linear models from Poisson family with robust standard errors to assess the association between high WHR levels and IR or Hyperinsulinemia after OGTT.

Outcomes	Variables	Crude PR (95% CI)	P value	Adjusted PR (95% CI)[a]	P value
IR	Normal WHR levels	Reference	–	Reference	–
	High WHR levels	2.65 (1.34–5.10)	0.004	2.63 (1.39–5.01)	0.003
Hyperinsulinemia after OGTT	Normal WHR levels	Reference	–	Reference	–
	High WHR levels	2.40 (1.05–5.51)	0.039	2.35 (1.03–5.38)	0.043

[a] Adjusted by: age (years), FT3 (pg/mL) and TSH (μU/mL).

Equally, the usefulness of WHR has also been tested for other metabolic disorders and CVDs [43–54], finding contradictory results. In this sense, some studies have found that WHR is a better screening measure for cardiometabolic conditions than other anthropometric indicators [46–49], while others reported that is not as useful as BMI, waist circumference (WC) or waist-to-height ratio (WHtR) [50–53]. In addition, an individual-participant meta-analysis of nine cohort studies conducted in the United Kingdom (UK) found no difference between WHR and other adiposity markers in the discrimination capacity of CVD mortality risk [54].

We only found two studies that explored the relationship between WHR and IR in apparently healthy individuals [22,55]. Although one of them was conducted in adolescents [55], both coincided in their results, finding a positive association between these two variables. Other studies have also found an association between high WHR levels and IR, but have included overweight or obese adults [56–58].

4.3. Results interpretation

IR is a complex metabolic disorder closely related to obesity [6–11] and directly interlinked with various inflammatory pathways [59,60]. In fact, different studies have reported an association between IR and C-reactive protein (CRP) [1], interleukin-6 (IL-6) [61], interleukin-1 beta (IL-1β) [62], tumor necrosis factor-alpha (TNF-α) [63] and other proinflammatory biomarkers [60,64,65]. Similarly, central obesity has been linked with increased plasma concentrations of these biomarkers and the generation of oxidative stress, which can lead to impaired insulin action [12,13,66].

On the other hand, studies in different ethnic populations have found that the association between VAT, IR and T2DM is notably stronger in women [67,68]. Then, evidence suggests that visceral fat accumulation might be particularly detrimental to them [24,25]; however, the explanation for this sex difference remains unclear. Women typically have more peripheral and less central fat than men [24,67], and it is, therefore possible that the excess of visceral fat accumulation in women could reflect an insidious onset or an advanced state of a metabolic disorder [24,25,67].

4.4. Relevance and implications

As previously mentioned, to date, the hyperinsulinemic-euglycemic clamp [32] and the HOMA-IR [33,34] are the most used methods for the diagnosis of IR. However, both have some limitations, mainly related to accessibility, cost, replicability and reproducibility [32,33,69,70]. Thus, anthropometric measures could arise as a good alternative for IR evaluation. In fact, due to their easy-to-measure characteristics and lower cost, they could be very useful for epidemiological studies and health basic attention services [29].

Different studies have highlighted the importance of the WHR as an anthropometric indicator for IR [22,37] and other cardiometabolic disorders [43–54]. Similarly, it has been tested in both normal-weight and obese individuals, different age groups and in both sexes [22,55,56,58]. Thus, WHR could be the anthropometric indicator of choice for early detection of IR, including in apparently healthy subjects.

Although WC is the anthropometric measure usually considered as the gold standard by clinical guidelines for the diagnosis of metabolic syndrome [71,72], it probably not be the most useful parameter if the evaluated population has a normal BMI or a short height. On the other hand, WHR indicates that central fat might be altered based on the hip circumference, having a better clinical correlation, a greater utility and a lower cost [22,37].

4.5. Limitations

Our study had some limitations. First, we did not assess causality between the evaluated variables due to the cross-sectional nature of our study. Second, we used information collected from medical records, which may have had some errors at the time of being filled; nevertheless, we conducted a rigorous evaluation of the data quality to reduce the possibility of information bias. Third, we used HOMA-IR to measure IR and not the hyperinsulinemic-euglycemic clamp (gold standard); however, HOMA-IR is the most widely used alternative and previous studies have shown a very high correlation between these two measures. Fourth, our study was conducted in a single private medical centre, thus our results cannot be generalized to the Hispanic women population; though, given the consistency of our findings with those described in other similar studies, we believe that they could be extrapolated to Hispanic euthyroid women with a normal BMI.

4.6. Conclusions

High WHR levels were associated with both IR markers used in our study, in a sample of euthyroid normal-weight women without T2DM. Prospective follow-up studies should corroborate these results using the gold standard and compare the WHR performance in both sexes. Additionally, we recommend that future studies contrast this indicator with other anthropometric measures, in order to determine the most appropriate one according to sex and age.

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Competing interests

The authors have no potential competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.11.043.

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