# Association Between Hyperinsulinemia and Endogenous Androgen Levels in Peri- and Postmenopausal Women

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**We evaluated the relationship between hyperinsulinemia and anthropometric, metabolic, and hormonal parameters that might contribute to the risk for coronary heart disease (CHD) in 104 peri- and postmenopausal women. Plasma glucose, insulin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), and total testosterone (TT) were determined. Free androgen index (FAI) and fasting insulin to glucose ratio (IGR) were calculated. The cut off point to define hyperinsulinemia was established at 23 $\mu$IU/mg. Mean age was 54.8 years. Mean age at menopause was 47.7 years. Body mass index (BMI) was greater than 25 in 46 patients, and 28 (26.9%) were hyperinsulinemic. BMI, waist circumference, triglycerides, and 2-hour postglucose insulin levels were significantly higher in hyperinsulinemic patients. Hyperinsulinemic patients had higher TT levels ($P = .02$), FAI ($P = .0001$), and lower SHBG levels ($P = .003$). Positive correlations were observed between IGR and BMI, waist-to-hip ratio (WHR), waist circumference, and triglycerides. IGR and high-density lipoprotein- cholesterol (HDL-C) were negatively correlated. IGR presented a positive association with TT and FAI and a negative association with SHBG. FAI contributed positively to IGR, independently of BMI, age, or time since menopause. In conclusion, androgen levels may be important determinants of risk factors for cardiovascular diseases in peri- and postmenopausal women. However, this observation should be confirmed by longitudinal studies.**


THE RISK FOR CORONARY heart disease (CHD) is lower in middle-aged women than in men.[1,2] However, this advantage, usually attributed to the levels of ovarian estrogen, disappears by the age of 75.[3,4] Estrogen is thought to exert cardioprotective effects both by lowering total and low-density lipoprotein-cholesterol (LDL-C) and by elevating high-density lipoprotein-cholesterol (HDL-C), as well as by acting directly on endothelial function.[5] Therefore, postmenopausal women, who do not produce significant amounts of estrogen, no longer benefit from such a protective effect.

Other hormonal and metabolic factors may also contribute to the development of CHD. For example, in states of insulin resistance and compensatory hyperinsulinemia, individuals are likely to develop a cluster of abnormalities that increase the risk for CHD.[6-9] In this context, we have recently studied the association between hyperinsulinemia and nitric oxide (NO) levels in healthy postmenopausal women.[10] Our preliminary results showed a strong negative association between insulin to glucose ratio (IGR) and NO levels in hyperinsulinemic postmenopausal women, suggesting that this may be 1 of the mechanisms by which the risk for CHD is increased.

The clinical association between insulin resistance, compensatory hyperinsulinemia, obesity, and hyperandrogenism is well recognized in premenopausal women with polycystic ovary syndrome.[11-13] In addition, a few studies have shown an association between insulin and androgen levels in premenopausal women with no evidence of clinical disease.[14,15] However, little attention has been given to this association in postmenopausal women,[16-18] a group at increased risk for CHD in relation to premenopausal women even in the absence of metabolic complaints. Therefore, our aim was to evaluate the relationship between hyperinsulinemia and anthropometric, metabolic, and hormonal parameters that might determine the risk factors for CHD in peri- and postmenopausal women.

## MATERIALS AND METHODS

### *Patients*

The study population included perimenopausal women (women who had entered menopause less than a year before the study) and postmenopausal women consulting consecutively during a 20 month-period for climacteric symptoms. The study was performed at the Gynecological Endocrinology Unit of Hospital de Clínicas de Porto Alegre, Brazil, to which patients were referred by general practitioners and gynecologists from primary care centers in the same city. Diabetic patients and patients with thyroid, hepatic, or renal dysfunction were excluded.

A total of 104 postmenopausal women were enrolled in the study. Inclusion criteria were as follows: (1) menopause, defined as last menstrual period at least 1 year before the beginning of the study or at least 6 months before the study plus follicle-stimulating hormone (FSH) levels higher than 35 IU/L; (2) more than 40 years of age; and (3) no use of any medication known to interfere with hormonal, glucose, or lipoprotein levels in the past 3 months. The study protocol was approved by the local Ethics Committee, and written, informed consent was obtained from every subject.

### *Study Protocol*

Anthropometric measurements included body weight, height, waist circumference (recorded at the narrowest point or at the umbilicus), hip circumference (recorded at the level of the greater trochanter), waist-to-hip ratio (WHR), and body mass index (BMI) (current weight measured in kilograms divided by height in meters squared). Blood pressure was measured after a rest period of 10 minutes with the woman in the supine position. The same calibrated mercury manometer

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attached to a 12.5 × 23 cm inflatable cuff was used in all patients by the same operator, who adopted the 5th Korotkoff sound to determine diastolic pressure. Hypertension was defined as systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, or current use of antihypertensive drugs.[19]

All studies were performed after a 3-day 300-g carbohydrate diet. Two blood samples were drawn from an antecubital vein for determination of plasma glucose and insulin: 1 after an overnight fast, and another 2 hours after the ingestion of 75 g of glucose. Blood samples were also drawn for luteinizing hormone (LH), FSH, sex hormone-binding globulin (SHBG), and total testosterone (TT) determinations. All samples were obtained between 8 and 10 AM.

Free androgen index (FAI) was estimated by dividing TT (nmol/L) by SHBG (nmol/L) × 100. To calculate fasting IGR ($\mu$IU/mg), fasting serum insulin was divided by fasting serum glucose, as previously reported.[20,21] The cut off point to define hyperinsulinemia was arbitrarily established at 23 $\mu$U/mg, taking into consideration the upper normal limit for insulin (25 mIU/mL) and for glucose (110 mg/dL), and confirmed by receiver operating characteristic curve analysis (ROC-curve).

Impaired glucose tolerance (IGT) was determined by glucose levels between 140 and 200 mg/mL on a 2-hour glucose tolerance test, as defined by the World Health Organization.[22,23]

### *Assays*

Total cholesterol, HDL, triglycerides, and glucose were determined by colorimetric-enzymatic methods using the Mega (Bayer, Leverkusen, Germany). LDL-C was determined indirectly using the formula LDL = total cholesterol - HDL + triglycerides/5. Serum LH and FSH were measured by specific immunofluorimetric assay (Wallac, Turku, Finland) with intra- and interassay coefficients of variation (CV) of 6.7% and 11%, respectively, for LH and 6.6% and 10.2% for FSH. The sensitivity of the assays was 0.12 IU/L for LH and 0.05 IU/L for FSH. TT levels were measured with the radioimmunoassay (RIA) method (DPC, Los Angeles, CA) with an assay sensitivity of 0.04 ng/mL, and intra- and interassay CV of 8.5% and 10.3%, respectively. SHBG was measured by chemiluminescent enzyme immunoassay (DPC), with an assay sensitivity of 0.2 nmol/L and intra- and interassay CV of 6.1% and 8.0%, respectively. Serum insulin levels were measured using a double antibody RIA (CIS Bio International, Bedford, MA), with an assay sensitivity of 2.0 mIU/mL, and intra- and interassay CV of 7.5% and 9%, respectively.

### *Statistical Analysis*

Results are presented as means ± SD or median and interquartile interval. Comparisons between the 2 group means were analyzed by Student's *t* test; comparisons between median values were analyzed using the Mann-Whitney *U* test. Spearman's rank or Pearson's correlation coefficients were calculated between variables using a 2-tailed significance test for variables with a gaussian or nongaussian distribution, respectively. A multiple regression model was also calculated to explore the relationship between IGR as a dependent variable and FAI, age, time since menopause, and BMI as independent variables.

All analyses were performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL). Data were considered to be significant at $P < .05$.

## RESULTS

The mean age of participants was 54.8 years, and the mean age at menopause was 47.7 years. BMI was greater than 25 in 46 patients (moderately overweight = 42.2%).. Thirty-seven patients (42%) were considered to have hypertension. Eighteen patients (19.7%) presented impaired glucose tolerance.

Table 1 shows clinical, anthropometric, and metabolic data for postmenopausal women. For the analysis of these data, patients were stratified into 2 groups according to IGR: normoinsulinemic (IGR ≤ 23 $\mu$IU/mL) and hyperinsulinemic patients (IGR > 23 $\mu$IU/mL). Among the 104 patients, 28 were defined as hyperinsulinemic (26.9%). BMI and waist circumference were significantly higher in hyperinsulinemic than in normoinsulinemic women. Regarding metabolic variables, triglycerides and 2-hour postglucose insulin levels were also higher in hyperinsulinemic patients in comparison with normoinsulinemic women.

Concerning hormonal levels, no differences were observed in LH and FSH between the 2 groups. As shown in Fig 1,

**Table 1. Clinical, Anthropometric, and Metabolic Parameters for Normo- and Hyperinsulinemic, Peri- and Postmenopausal Women**

| | Normoinsulinemic Group IGR ≤ 23 $\mu$IU/mg (n = 76) | Hyperinsulinemic Group IGR > 23 $\mu$IU/mg (n = 28) | *P* |
|---|---|---|---|
| Age (yr) | 54.7 ± 6.3 | 54.9 ± 5.62 | .868 |
| Age at menopause (yr) | 47.5 ± 4.7 | 48.1 ± 4.3 | .545 |
| Time since menopause (yr) | 4.9 (2.6-11) | 5 (2.3-9.15) | .461 |
| BMI (kg/m$^2$) | 27.1 ± 4.8 | 29.2 ± 3.5 | .034 |
| Waist circumference (cm)* | 85 (79.7-95.0) | 88 (83.5-94.0) | .046 |
| WHR | 0.84 ± 0.06 | 0.86 ± 0.05 | .177 |
| Systolic blood pressure (mm Hg) | 128.4 ± 21.81 | 128.86 ± 21.4 | .931 |
| Diastolic blood pressure (mm Hg) | 78.8 ± 11.2 | 82.71 ± 14.1 | .152 |
| Fasting glucose (mg/dL) | 91.2 ± 11.3 | 89.3 ± 8.7 | .425 |
| 2-hour glucose (mg/dL) | 114.3 ± 30.6 | 121.5 ± 40.09 | .370 |
| Total cholesterol (mg/dL) | 235.1 ± 36.5 | 238.2 ± 38.62 | .698 |
| HDL-C (mg/dL) | 56.1 ± 12.9 | 51.39 ± 9.48 | .079 |
| LDL-C (mg/dL) | 155.2 ± 36.1 | 154.4 ± 34.2 | .905 |
| Triglycerides (mg/dL)* | 108 (72.5-137.5) | 135 (105-191) | .010 |
| Fasting insulin (mIU/mL)* | 13.9 (11.2-17.5) | 24.8 (23.0-29.9) | .000 |
| 2-hour insulin (mIU/mL)* | 55.8 (35.1-93.7) | 105 (48-194.5) | .005 |

NOTE. Values are expressed as mean ± SD (Student's *t* test) or *median and interquartile range (25% to 75%) (Mann-Whitney *U* test).

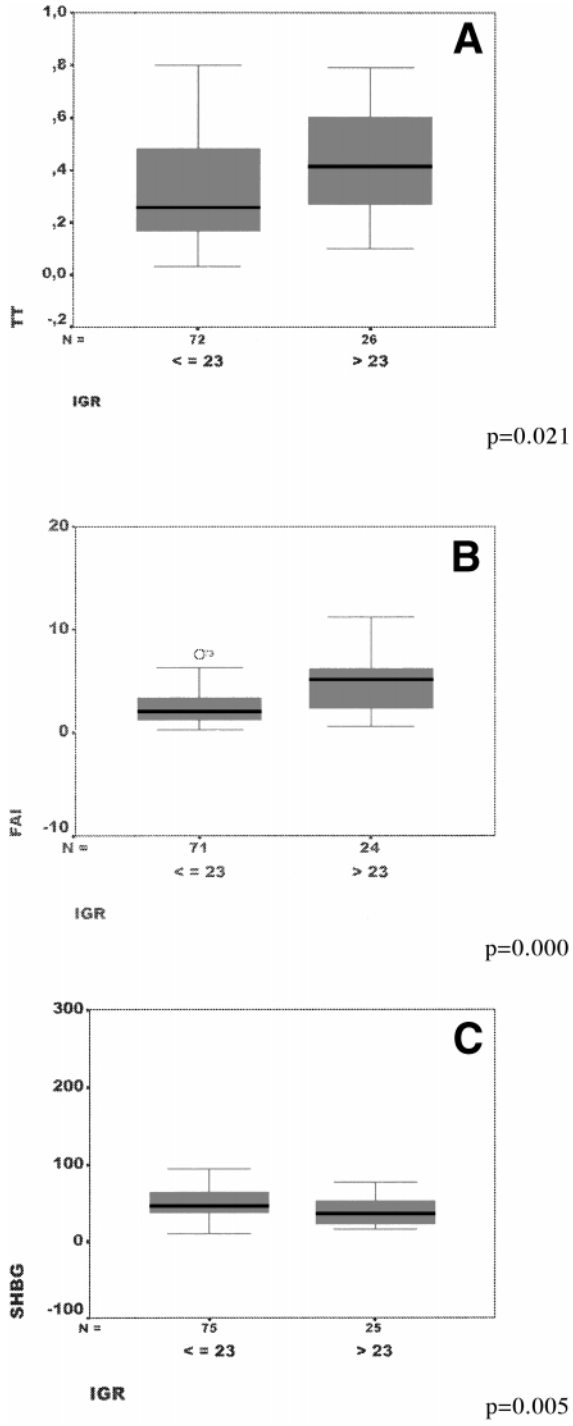


**Fig 1. Hormone levels in normo- and hyperinsulinemic, peri- and postmenopausal women. (A) TT concentrations, (B) FAI, and (C) SHBG levels. The line across each box represents the median, whereas the upper and lower lines of the box show the interquartile range. The upper and lower lines outside the box show maximal and minimal values.**

hyperinsulinemic patients had higher TT ($P = .02$, Fig 1A) and FAI ($P = .0001$, Fig 1B) and lower SHBG levels ($P = .003$, Fig 1C).

Table 2 shows the association between IGR and anthropometric, metabolic, and hormonal variables for the entire group (n = 104) and for hyperinsulinemic (n = 76) and normoinsulinemic (n = 28) postmenopausal women. Significant positive correlations were observed between IGR and BMI, WHR, waist circumference, and triglycerides. A negative correlation was observed between IGR and HDL-C. IGR presented a significant positive association with TT and FAI (Table 2 and Fig 2A) and a significant negative association with SHBG (Table 2 and Fig 2B).

Taking into consideration the results of the linear regression analysis, in which a positive correlation between IGR and FAI was observed, a multiple regression model was set up with IGR as the dependent variable to test the hypothesis that the levels of FAI might be influencing the levels of IGR (Table 3). This analysis also aimed at eliminating the influence of obesity, age, and time elapsed since menopause as possible confounding factors, and therefore BMI, age, and time since menopause were included as independent variables.

As shown in Table 3, FAI contributed positively and significantly to IGR, independently of BMI, age, or time since menopause.

## DISCUSSION

The average age of the population in the present study (54.8 years) was similar to that of previous studies.[16,17] Although amenorrhea duration was not an exclusion criterion, median amenorrhea duration was 5 years, ie, within the first (initial) years of menopause. Previous studies have excluded patients with amenorrhea lasting for more than 5[24] and 10 years.[25] Similar to several investigations, we characterized menopause as at least 1 year of amenorrhea.[17,18,26] However, we also included patients with at least 6 months of amenorrhea; in these cases, we adopted an additional inclusion criterion, ie, FSH levels greater than 35 UI/L, as proposed by Sites et al.[27] Therefore, we define the present sample as including both peri- and postmenopausal women.

In this study, both insulin and IGR were used as markers of insulin sensitivity. Previous reports have shown that in nondiabetic subjects, fasting insulin is closely correlated with more direct measures of insulin resistance.[28] Moreover, IGR or glucose to insulin ratio have also been shown to be useful measures of insulin resistance in women with polycystic ovary syndrome (PCOS).[10,20,29,30] In our population, 26% of the women were considered hyperinsulinemic, with an IGR higher than 23 $\mu$IU/ml.

SHBG levels may also be markers of insulin resistance in humans.[31] The concentration of SHBG is an indirect indicator of the relative androgen/estrogen balance, ie, decrease in SHBG results in a change in the relative androgen/estrogen balance in the direction of androgen. Our hyperinsulinemic patients presented lower median levels of SHBG in relation to normoinsulinemic patients; a bivariate analysis showed a negative association between SHBG and IGR, in agreement with previous studies.[17,32]

In the present study, we examined the hypothesis that hyperinsulinemia, a risk factor for CHD, might be related to endogenous androgen levels in postmenopausal women in the

**Table 2. Correlation Between IGR and Anthropometric, Metabolic, and Hormonal Variables**

| Variable | Correlation Coefficient Entire Group | *P* | Normoinsulinemic (n = 76) | *P* | Hyperinsulinemic (n = 28) | *P* |
|---|---|---|---|---|---|---|
| Age | *r* = .06 | .518 | *r* = .073 | .531 | *r* = .113 | .566 |
| Age at menopause | *r* = .052 | .605 | *r* = .055 | .639 | *r* = −.121 | .548 |
| Time since menopause | rs = −.06 | .533 | rs = −.17 | .886 | rs = .012 | .954 |
| BMI | *r* = .298 | .002 | *r* = .178 | .125 | *r* = .390 | .04 |
| Waist circumference | *r* = .254 | .010 | *r* = .121 | .303 | *r* = .482 | .009 |
| WHR | *r* = .213 | .031 | *r* = .00 | .998 | *r* = .629 | .000 |
| Total cholesterol | *r* = .02 | .839 | *r* = .004 | .971 | *r* = −.065 | .744 |
| HDL-C | *r* = −.21 | .028 | *r* = −.127 | .275 | *r* = −.153 | .437 |
| LDL-C | *r* = −.07 | .472 | *r* = −.078 | .514 | *r* = −.174 | .396 |
| Triglycerides | rs = .363 | .000 | *r* = .300 | .009 | *r* = .344 | .073 |
| TT | rs = .23 | .022 | rs = .077 | .523 | rs = .334 | .095 |

NOTE. *r,* Pearson correlation coefficient; rs, Spearman's rank correlation coefficient.

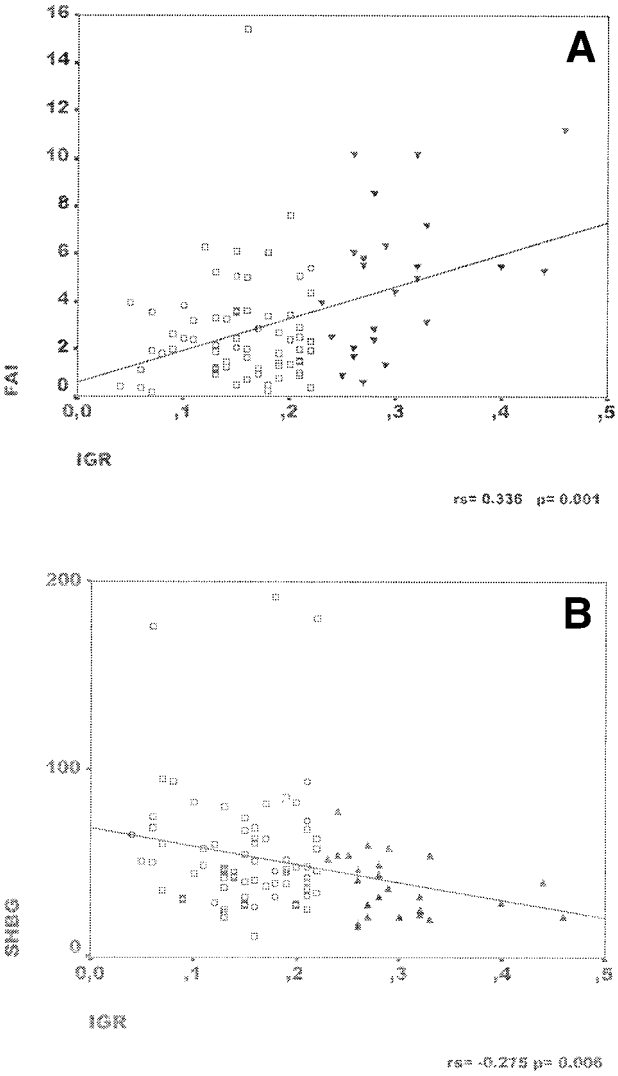


**Fig 2. (A) Correlation between IGR and FAI in the study population (n = 104) and (B) correlation between IGR and SHBG in the study population (n = 104). □, Normoinsulinemic women; ▲, hyperinsulinemic women.**

absence of overt clinical disease, as shown for premenopausal women.[14] Our data indicate that such a relationship exists throughout the physiologic range of total and free testosterone levels, below any clinically defined abnormal levels. Which abnormality (hyperinsulinemia or altered androgen levels) may be causal is not yet clear. However, it could be that androgens increase central adiposity, leading to insulin resistance and increased insulin levels.[33,34] In addition, sex hormones seem to have a role in controlling insulin receptors.[35,36] On the other hand, hyperinsulinemia has been shown to increase the production of androgens through the ovaries,[37] and it may suppress the production of SHBG in the liver.[38] In obese women with PCOS, the reduction of insulin levels with metformin was associated with an improvement in hyperandrogenism.[39]

There is evidence that androgens play a role in the metabolism of glucose and insulin resistance, and they might mediate some of the cardiovascular consequences of insulin resistance, even in postmenopausal women. A population-based study[34] showed a positive association between fasting glycemia levels and dehydroepiandrosterone sulfate (DHEA-S) and a negative association between fasting glycemia and SHBG. Haffner et al[17] have also shown a negative correlation between SHBG levels and triglycerides and insulin and a positive correlation between SHBG and HDL-C levels in 101 postmenopausal women. After adjustment for BMI and WHR, SHBG levels remained negatively associated with insulin and positively associated with HDL-C. In that study, SHBG levels were not associated with blood pressure. Another study by Haffner et al[18] also showed an association between androgen levels and other risk factors for cardiovascular disease in postmenopausal women. TT levels were positively and significantly correlated

**Table 3. Model-Fitting Results for Multiple Regression of IGR Versus Age, Time Since Menopause, FAI, and BMI**

| Independent Variables | Dependent Variable: IGR Coefficient | *P* |
|---|---|---|
| Age | −.009 | .949 |
| Time since menopause | −.022 | .871 |
| FAI | .366 | .000 |
| BMI | .250 | .011 |
| $R^2$ = .233 | | |

with total cholesterol and systolic and diastolic blood pressure and inversely correlated with the HDL-C to total cholesterol ratio. Free testosterone levels were significantly and inversely correlated with HDL-C and with the HDL-C to total cholesterol ratio.

In a recent study of premenopausal women with regular cycles, Ivandíc et al[14] observed a positive correlation between free testosterone and fasting insulin levels. However, that correlation was dependent on other variables, such as BMI and SHBG. Because our sample was more homogeneous and the patients were stratified by IGR only after inclusion in the study, we were able to show a significant association between androgen levels and IGR – independently of age, menopause time, and obesity – in postmenopausal patients, a group with increased incidence of cardiovascular disease.

Our hyperinsulinemic patients presented higher BMI, waist circumference, triglycerides, and circulating androgen levels, as well as lower concentrations of SHBG. The results of several studies support the importance of waist circumference as an anthropometric variable to identify patients at higher risk for metabolic alterations. Obesity, in general, but especially central distribution of body fat, is associated with insulin resistance.[25] Similarly, a study by Ross et al[40] including obese premenopausal women (BMI $>$ 27 kg/m$^2$) showed a strong correlation between waist circumference, fasting insulin, and area under the insulin curve. Haffner[41] showed that weight, BMI, waist circumference, and WHR are positive predictors of type 2 diabetes regardless of age and sex; on multivariate analysis, waist circumference was the only significant predictor of diabetes in a model including other anthropometric variables. Epidemiologic studies have also shown that hyperinsulinemia and insulin resistance are associated with metabolic alterations, such as increase in triglycerides and LDL-C, and decrease in HDL-C.[9,42,43] Although within normal limits, the increased levels of triglycerides observed in our hyperinsulinemic patients support these findings.

The effect of the transition to menopause on insulin sensitivity is not well established. Berger et al[44] showed that the levels of insulin were significantly lower in premenopausal women than in postmenopausal women. Matthews et al,[45] however, showed that natural menopause did not affect insulin and glucose plasma levels. In addition, Peters et al[26] found no statistically significant difference between the insulin levels of 93 premenopausal and 93 age-matched postmenopausal patients. In a different study, postmenopausal women presented an increase in fasting insulin levels in comparison with age-matched premenopausal women.[46]

Although in the present study our objective was not to assess the role of menopause on insulin resistance per se, the lack of statistical difference between normo- and hyperinsulinemic patients concerning age, age at menopause, and time since menopause suggests that these factors do not influence insulin sensitivity. In addition, we observed that age and time elapsed since menopause were not associated with IGR. A similar result was found by Barret-Connor et al[16] in a large study assessing 869 postmenopausal women. Those investigators observed a significant age-related increase of plasma glucose that was not observed for insulin. In addition, the association between obesity and increased cardiovascular risk is well established in both men and women.[47,48]

In conclusion, our data indicate an association between hyperinsulinemia and serum androgen levels in peri- and postmenopausal women with no evidence of clinical disease. The present results support the notion that androgen levels may be important determinants of risk factors for cardiovascular disease. However, longitudinal studies are still required to confirm the actual role of androgens in determining cardiovascular risk.

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