Relationship between insulin and hypogonadism in men with metabolic syndrome

Relação entre insulina e hipogonadismo em homens com síndrome metabólica

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ABSTRACT

Objective: To evaluate the incidence of hypogonadism in men with metabolic syndrome and its correlation with serum insulin levels. **Methods:** Observational, transversal study with 80 men with metabolic syndrome. The individuals were divided into two groups: Group 1: 56 patients (70%) with total testosterone ≥ 300 ng/dL (normal gonadal function); Group 2: 24 patients (30%) with total testosterone < 300 ng/dL (hypogonadic). **Results:** The subjects from Group 2 compared to Group 1 presented higher body mass index (BMI), waist and hip circumferences, insulin, homeostasis model assessment insulin resistance index (Homa-IR) and beta cell (Homa-β), and triglycerides, but lower SHBG and free testosterone values. Inverse correlations between insulin levels and total testosterone and SHBG, as well as between Homa-IR and total testosterone were observed. **Conclusion:** In this series of men with metabolic syndrome, hypogonadism was associated with insulin resistance and may be a marker of metabolic abnormalities. Arq Bras Endocrinol Metab. 2009;53(8):1005-11

Keywords
Metabolic syndrome; insulin resistance; hypogonadism; male; testosterone

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RESUMO

Objetivo: Avaliar a frequência de hipogonadismo em homens portadores da síndrome metabólica e a sua correlação com a concentração sérica de insulina. **Métodos:** Estudo observacional e transversal com 80 homens portadores da síndrome metabólica. Os sujeitos foram estratificados em dois grupos: Grupo 1: 56 pacientes (70%) com testosterona total ≥ 300 ng/dL (função gonadal normal); Grupo 2: 24 pacientes (30%) com testosterona < 300 ng/dL (hipogonádicos). **Resultados:** Os sujeitos do Grupo 2 comparados ao Grupo 1 tinham maior índice de massa corporal (IMC), de circunferências do quadril e da cintura, insulina, Homa-IR, Homa-β e triglicerídeos, mas tinham valores menores de SHBG e testosterona livre. Observou-se correlação inversa da concentração de insulina com a de testosterona total e SHBG, e do Homa-IR com a concentração de testosterona total. **Conclusão:** Nos indivíduos estudados, a presença de hipogonadismo esteve associada à resistência à insulina, podendo ser um marcador de alterações metabólicas. Arq Bras Endocrinol Metab. 2009;53(8):1005-11

Descritores
Síndrome metabólica; resistência à insulina; hipogonadismo; masculino; testosterona

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INTRODUCTION

Metabolic syndrome is currently one the most common metabolic disorders, considered as the most important risk factor for the occurrence of cardiovascular diseases. It is characterized by alterations in carbohydrate metabolism, obesity, systemic arterial hypertension and dyslipidemia (1).

Metabolic alterations associated with this syndrome affect different neuroendocrine axis controlled by the hypothalamus and the pituitary (1-3). In the gonado-

trophic axis, metabolic syndrome is associated with a state of male hypogonadism, whose origin and precise physiopathological mechanisms are still unknown (1,4).

The hyperinsulinemic state inherent to the metabolic syndrome leads to inhibition of the hepatic production of steroid hormone binding globulin (SHBG), with a consequent decrease in the total testosterone levels. However, the free testosterone levels may remain normal or reduced, depending on the severity of obesity (1-3). Several theories have been proposed to explain the decrease in the total and free testosterone levels, including the direct inhibition of testicular production by insulin and leptin, elevation of estrogen concentrations and alteration in the secretion of gonadotrophins (1,4-7).

Alternatively, there are evidences that testosterone is an important regulator of insulin sensitivity in men; low concentrations of androgens are associated with several components of metabolic syndrome, including coronary artery disease, hypertension, dyslipidemia, a prothrombotic state and visceral obesity (5-9).

The diagnosis and treatment of hypogonadism in males are important issues, considering that testosterone deficit is related to sexual dysfunction, depressed humor, irritability, concentration disturbance, weakness, fatigue, decrease in well-being and quality of life, osteoporosis and changes in corporal composition (6-9).

In this paper, we have systematically evaluated the gonadal function from metabolic syndrome male carriers, with emphasis on determining the frequency of hypogonadism and its relation to serum insulin levels.

METHODS

The study consisted of an observational and transversal evaluation of 80 male patients with metabolic syndrome, who was under treatment at the University Hospital of Brasília, in the period from January 2003 to March 2007. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine of the University of Brasília. All participants have signed an Informed Consent Form. There was no conflict of interests.

The diagnosis of metabolic syndrome was based on the presence of three or more of the following criteria (10,11): 1) waist circumference > 94 cm; 2) altered fasting glucose levels (venous fasting glucose levels ≥ 100 mg/dL) or intolerance to oral glucose (glycemia > 140 and < 200 mg/dL 120 min after the ingestion of 75 g of dextrosol) or *diabetes mellitus* (two fasting glucose levels ≥ 126 mg/dL, or one randomly performed glycemia > 200 mg/dL associated with typical diabetic symptoms, or glycemia 120 min after the ingestion of 75 g of dextrosol > 200 mg/dL); 3) triglycerides > 150 mg/dL; 4) HDL-cholesterol < 40 mg/dL; 5) arterial blood pressure > 130/85 mmHg.

Patients with metabolic syndrome were excluded from the study when they had: 1) low levels of free and total testosterone associated with high concentrations of FSH and LH, characterizing andropause or primary gonadal insufficiency; 2) altered prolactin and/or TSH levels; and/or 3) Cushing's syndrome (that was excluded when plasma cortisol levels were lower than 1.8 µg/dL at 8.00 p.m. after the intake of 1.0 mg of dexamethasone at 11.00 p.m. on the previous day) (12).

Selected patients were divided into two groups according to the levels of total testosterone: Group 1: ≥ 300 ng/dL (preserved gonadal function); Group 2: < 300 ng/dL (hypogonadic).

The following clinical parameters were assessed: body mass index (BMI), calculated by the formula weight (kg)/height $(m)^2$; measurements of the waist and hip circumferences, taken, respectively, at the umbilical scar and trochanters levels, with the use of a measuring tape; arterial blood pressure taken from left arm extended at the level of the precordium, using a mercury sphygmomanometer.

Blood samples were collected between 7 and 9 a.m. after a 12-hour night-fasting. The blood was centrifuged at 3,000 rpm for 10 minutes and the serum was stored at -20°C until assayed. Triglycerides and glucose assays were performed immediately after blood was drawn, so that no degradation would occur from the freezing process.

The following laboratory evaluations were conducted by means of commercial kits (normal range values are presented in parenthesis): fasting glucose (70-100 mg/dL), by oxidasis-GOD/POD-automatized; fasting insulin (2.5-14.8 µUI/mL, by a chemiluminescent assay); triglycerides, total cholesterol and HDL-cholesterol (< 150 mg/dL, < 200 mg/dL and > 40 mg/dL, respectively), by magnesium phosphate; FSH, LH, TSH and prolactin (4 to 13 mUI/mL, 1 to 18 mUI/mL, 0.35-4.94 µUI/mL, and 1.2-17.5 ng/mL, respectively), by microparticle-based chemiluminescence; total (260-1000 ng/dL) and free (8.7-54.7 pg/mL) testosterone, and SHBG (13-71 nmol/L) by chemiluminescence; cortisol (< 1.8 µg/dL after ingestion of 1.0 mg of dexamethasone at 11 p.m. on the previous day) by electrochemiluminescence.

The Homeostasis Model Assessment Insulin Resistance Index (Homa-IR) was calculated using the following formula (13): Homa-IR = [fasting insulin (μU/mL) x glucose (mmol/L)]/22.5. For the Brazilian population, this index defines the degree of insulin resistance, as abnormal if > 2.7 (14). The Homa-β index, which defines the function of the beta cell, was calculated by the formula (13): Homa-β = 20 x insulin (μU/ml)/(glucose (mmol/L). Values between 81 and 227 are considered normal.

Statistical analysis

Student's t-test was used for comparison between groups for the aspects presenting Gaussian distribution: age, weight, BMI, hip and waist circumferences. Mann-Whitney's non-parametric test was used for the data which did not present Gaussian distribution: glucose, insulin, Homa-IR, Homa-β, cholesterol, triglycerides, HDL-cholesterol, FSH, LH, SHBG, total and free testosterone.

A multiple linear regression model was adjusted to assess how the presence or absence of hypogonadism, BMI, hips, waist, insulin, Homa-IR, Homa-β, cholesterol, triglycerides, HDL-cholesterol, FSH, LH and total testosterone may influence in the behavior of SHBG, total and free testosterone.

Statistical analysis was performed using the SAS software, version 9.1.3. The results are presented as average values and standard deviation.

RESULTS

Eighty patients, aged 42 ± 12 years old on average (range, 18 to 65 years), entered the study. Group 1 was composed of 56 patients (70%) and Group 2 had 24 patients (30%).

The clinical profiles of both groups are shown in table 1. Hypogonadic patients (Group 2) had significantly higher BMI, waist and hip circumferences values than those of Group 1, but no significant differences in weight and age were found.

As shown in table 2, patients from Group 2 had SHBG, free and total testosterone levels significantly lower than those from Group 1, but no statistically significant differences on the FSH and LH levels were found between groups. However, insulin and triglycerides levels, Homa-IR, and Homa-β were significantly higher in Group 2 than in Group 1, but no statistically significant differences in the glucose, total cholesterol, and HDL-cholesterol levels were observed between the groups.

Table 1. Clinical profile of 80 men with metabolic syndrome, and normal (group 1) or low (group 2) testosterone levels

Variable	Groups		p
	1 (n = 56)	2 (n = 24)	
Age (year)	40.4 ± 13	42.4 ± 9.2	0.5
Weight (kg)	98.3 ± 16.2	108.2 ± 25.9	0.09
BMI (kg/m²)	31.9 ± 4.9	34.7 ± 6	0.03
Hip (cm)	108.2 ± 11.7	118.6 ± 18.9	0.01
Waist (cm)	107 ± 12.1	117.5 ± 16.8	0.009

p < 0.05; BMI: body mass index; Student´s t test.

Table 2. Laboratorial characteristics of 80 men with metabolic syndrome, and normal (group 1) or low (group 2) testosterone levels

Variable	Groups		p
	1 (n = 56)	2 (n = 24)	
Total testosterone (ng/dL)	455.7 ± 131.9	227.7 ± 38.3	0.001
Free testosterone (pg/mL)	19.1 ± 10.1	15.5 ± 17	0.004
SHBG (nmol/L)	18.6 ± 10.1	7.9 ± 4.2	0.001
FSH (mUI/mL)	3.8 ± 2.5	5.5 ± 5.6	0.34
LH (mUI/mL)	2.9 ± 1.6	3.6 ± 2.2	0.16
Glucose (mg/dL)	100.7 ± 30.6	99.5 ± 16.1	0.1
Insulin (μUI/mL)	12 ± 8.3	21.5 ± 10	0.001
Homa-IR	3.1 ± 2.6	5.3 ± 2.6	0.003
Homa-β	145.6 ± 110.3	230.9 ± 114.6	0.001
Total cholesterol (mg/dL)	191.4 ± 34.1	196.9 ± 34.1	0.6
HDL-cholesterol (mg/dL)	44.5 ± 11.4	42.1 ± 6.7	0.4
Triglycerides (mg/dL)	165.7 ± 100.7	206.6 ± 94.4	0.02

p < 0.05; SHBG: sex hormone-binding globulin; FSH: follicle-stimulating hormone; LH: luteinizing hormone; Mann-Whitney test.

In the adjustment of the multiple linear regression model, insulin had a significant and inversely proportional effect on total testosterone (p = 0.04) and SHBG levels (p = 0.03), but not on free testosterone levels (p = 0.65); Homa-IR had a significant and inversely proportional effect on total testosterone levels (p = 0.02), but not on free testosterone (p = 0.50) and SHBG levels (p = 0.06); and Homa-β did not correlate with any of them: total (p = 0.13) and free (p = 0.82) testosterone, and SHBG levels (p = 0.10).

As presented in figure 1, the variables insulin concentration and group were significantly correlated (p = 0.04) with total testosterone, as follows: in Group 1, for the increment of each unit in the insulin levels, the average testosterone level decreased 0.05 units, and, in Group 2, for the increment of each unit in the insulin levels, the average total testosterone decreased 5.69 units. Moreover, it was observed that the patients from

Group 2 had an average decay in total testosterone that was 5.64 units superior to that of Group 1 patients, with a 95% confidence interval ranging from -11.26 to -0.02.

As shown in Figure 2, the SHBG correlated, inversely and significantly, with insulin levels (p = 0.03) and group (p = 0.01) (test F = 15.1; p < 0.01), as follows: for the increment of each unit in the insulin levels, the average levels of SHBG decreased 0.25 units, for both groups: Group 1, without hypogonadism, presented average SHBG concentrations 8.2 units higher than those of the group with hypogonadism, with a 95% confidence interval ranging from 3.46 to 13.05.

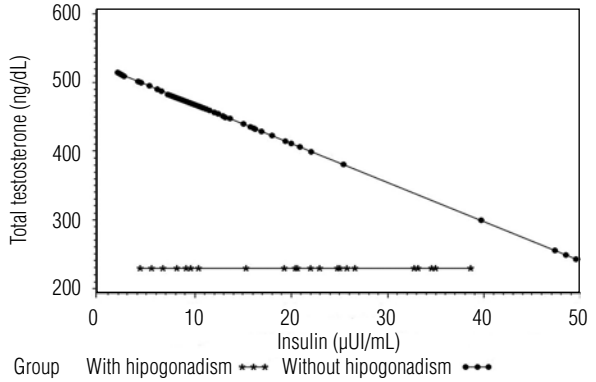

Figure 1. Multivariate analysis, showing the inverse significant correlation of the variables insulin concentration and group with total testosterone levels, in both groups of patients (p = 0.04).

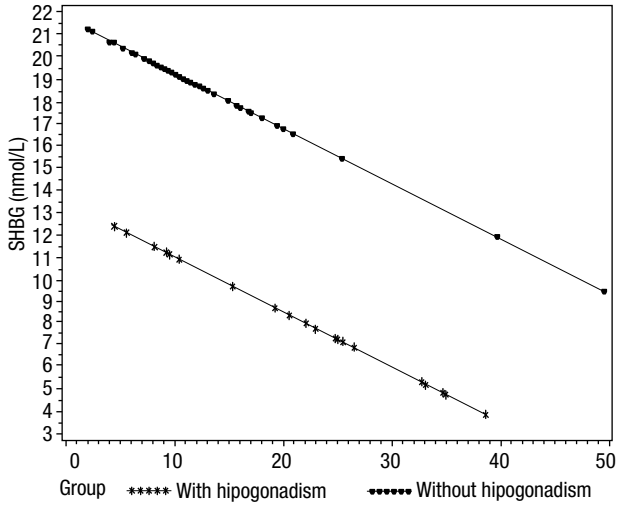

Figure 2. Multiple linear regression for SHBG in relation to insulin and groups with and without hypogonadism, showing that SHBG levels are inversely and significantly correlated to insulin levels (p = 0.03), in both groups.

DISCUSSION

In this series of men with metabolic syndrome, we found a high frequency (30%) of hypogonadism, which is mainly characterized by low concentrations of total testosterone (< 300 ng/dL). Most investigators consider 300 mg/dL as the lower limit for normality, since inferior values are associated with symptoms and clinical alterations compatible with hypogonadism (9).

A frequency of 33% of hypogonadism was found in another systematic evaluation of 103 men with diabetes, a rate similar to that found in the present study. However, a variation of 20% to 64% in the frequency of low androgen levels was found when assessing men with *diabetes mellitus* and metabolic syndrome (9).

Previous data has shown that the age of the study population may influence the frequency of testosterone deficiency. For example, in one series, testosterone levels lower than 300 ng/dL were observed in 64% of the diabetic patients, and 38% of the non-diabetic ones, when the subject's age was higher than 73 years old (15). On the other hand, when the age of the patients ranged from 40 to 79 years old, low levels of testosterone were observed in 21% of the diabetic men, and 13% of the non-diabetic (16). However, in the present study, the patients pertaining to both groups had similar average ages (40 and 42, for individuals without and with hypogonadism, respectively). Such relatively young ages are not commonly associated with a high frequency of hypogonadism (17,18), which suggests that age had not specifically interfered on the results.

The decrease in testosterone levels associated with age can be precluded in healthy men, that is, in those men with no evidence of chronic diseases and/or who have a healthy life style (17). Indeed, a significant number of men remain eugonadic even at advanced ages (18). Nevertheless, patients with chronic diseases have a higher risk of having their testosterone levels diminished. A prevalence of 38.7% of hypogonadism, defined as testosterone levels under 300 ng/dL, was found in 2,162 patients with 45 or more years of age who received attention in primary care clinics in the United States (19). The authors of the cited paper observed that chronic diseases such as arterial hypertension, hyperlipidemia, prostate disease, asthma or chronic obstructive pulmonary disease, and, mainly, obesity and type 2 *diabetes mellitus* were associated with a higher risk of hypogonadism (19).

We observed a significantly higher BMI, hip and waist circumferences, and a tendency, albeit not statistically significant, to a higher weight in hypogonadic patients (Group 2), as compared to the group of patients without hypogonadism (Group 1). These find-

ings suggest that a larger accumulation of abdominal fat is associated with a higher frequency of hypogonadism. These results are in accordance to those found by other authors who have also demonstrated that higher levels of BMI and a centripetal distribution of body fat are associated with low concentrations of testosterone (7,20-24). Besides that, in a study about the prevalence of low testosterone levels (inferior to 300 ng/dL) in men, obesity was associated with the highest odds ratio (2.38) for hypogonadism, as compared to other comorbid conditions evaluated (19).

The reasons for the association between metabolic syndrome and hypogonadism are not completely clear. It has been suggested that insulin resistance, acting through signs mediated by the adipose tissue, including increased levels of leptin, would have a direct role in the regulation of gonadal function, thus decreasing the concentrations of testosterone (1,4,25,26). At the same time, pro-inflammatory cytokines, such as TNF alpha, IL-1 and IL-6, produced by visceral adipocytes, are also associated with insulin resistance (27,28). It was demonstrated that there is a strong correlation between insulin sensitivity and the function of Leydig's cell (29), but other studies have not confirmed such findings (23,30).

Our results point to a possible association between insulin resistance and hypogonadism, since the concentrations of basal insulin, the insulin resistance index (Homa-IR) and the index that measures the pancreatic beta cell function (Homa-β) were significantly higher in the hypogonadic group as compared to the eugonadic group. These results are in accordance to the previous observation of an inverse correlation between fasting insulin and testosterone levels (22,24). Moreover, male patients with insulin resistance-associated diseases, such as obesity (20-24) and type 2 *diabetes mellitus* (31), have levels of testosterone lower than control patients with normal weight who are not diabetic. Transversal studies have also demonstrated an inverse correlation between testosterone and fasting insulin levels in men, regardless of age, obesity and fat distribution (20,21,25,31).

We have also found significantly lower SHBG levels in hypogonadic patients and an inverse correlation between insulin and SHBG. It means that high levels of insulin corresponded to low levels of SHBG, inasmuch as that every one-unit increase in the levels of insulin resulted in a 0.25 unit decrease in the average SHBG levels, in both groups. A similar decrease in the SHBG levels in hypogonadic patients has been previously described in individuals with metabolic syndrome and is associated with insulin resistance, carbohydrate intolerance and central obesity (23,32-36). It has been suggested that SHBG concentration could be used as a specific marker of insulin resistance as well as one of the components of the metabolic syndrome (37,38).

The increase in insulin levels observed in metabolic syndrome carriers is probably secondary to the insulin resistance action, and may develop as a means to overcome this defect. Our results are in compliance with this hypothesis, since we noted an increase in both the insulin resistance index (Homa-IR) and the index that measures pancreatic beta cell function (Homa-β) in hypogonadic patients. The pathological increase in Homa-β possibly represents an attempt to overcome the insulin resistance action by enhancing the function of the pancreatic beta cell. This hypothesis is also reinforced by the fact that increased testosterone levels were observed during the hyperinsulinemic state of the clamp glucose test (29,39).

However, the precise mechanisms involved in insulin action that result in low testosterone and SHBG levels are not clear yet, but might be due to a functional defect at one or more levels of the hypothalamus-pituitary-gonadal axis (29).

It is known that insulin plays a relevant role in the central regulatory systems involved in reproductive function, acting synergistically to various factors to mediate the secretion of gonadotrophins and the control of body weight (40). Insulin is also involved in the pathophysiology of obesity following lesions to the hypothalamus-pituitary region (41). It has been suggested that obese patients with insulin resistance have a diminished sensitivity to insulin action in the hypothalamus-pituitary-gonadal axis due to the production of cytokines and hormones by the adipose tissue (29). However, in the present study, the gonadotrophins levels were similar in both groups, suggesting that the hypothalamus and pituitary had no influence on the lower levels of testosterone observed in the hypogonadic group. Similarly, other authors have found no correlation between insulin sensitivity and basal, GnRH- or clomiphene-stimulated LH secretion (29,30). Nevertheless, the concentrations and pulse amplitude of LH may be abnormal in morbid obesity patients (41-43).

It has been suggested that an increased abdominal adipose tissue deposition in hypogonadic patients would generate a vicious cycle, in which the excessive aromatase activity would enhance the conversion of

testosterone into estradiol. This would inhibit gonadotrophin production centrally, and further decrease testosterone levels. Subsequently, the decrease in testosterone would facilitate a higher deposition of body fat and a more severe degree of hypogonadism (1,7,44).

On the other hand, there is evidence that a low testosterone level in men would result in insulin resistance and abdominal obesity, as well as be a predictive factor for the development of type 2 *diabetes mellitus* (6,45-49). It has been proposed that the hypogonadism resultant from prostate cancer treatment, by the blockage of gonadotrophins by GnRH-agonists (50,51) or by castration (52), could be associated with an increase in insulin levels.

Moreover, multiple interventional studies have shown that exogenous testosterone has a favorable impact on body mass index, insulin secretion and sensitivity, lipid profile and blood pressure, which are the parameters that are often disturbed in metabolic syndrome. Testosterone supplementation was able to reduce abdominal circumference and waist-hip ratio, and to improve insulin sensitivity and glycemic control in men with hypogonadism and type 2 *diabetes mellitus* (6,8,53,54). Testosterone replacement was also able to decrease the levels of pro-inflammatory cytokines (TNF-alpha, IL-1 and IL-6) produced by visceral adipocytes and associated with insulin resistance (27,55). Although the impact of these findings on an individual's cardiovascular risk have not been systematically investigated, concomitant improvements in glycemic control, insulin resistance, lipid profile and visceral adiposity probably represent an overall reduction in cardiovascular risk. Prospective long-term clinical trials are necessary to clarify this issue.

The observation of low levels of HDL-cholesterol is one of the diagnostic criteria for metabolic syndrome. We have not found a significant difference in HDL-cholesterol levels nor in total cholesterol levels in either group of patients. These results might be interpreted based on the previous observations that testosterone supplementation can decrease total cholesterol levels without affecting HDL-cholesterol levels (53,55).

In summary, there is sufficient evidence that reductions in SHBG and total and free testosterone levels might be related to high concentrations of insulin, secondary to insulin resistance, as demonstrated in the present study (5,21,29). On the other hand, the state of hypogonadism would favor, by itself, the development of insulin resistance, central obesity, type 2 *diabetes mellitus* and increased cardiovascular risk (8,37,38,54,56).

In conclusion, our results demonstrate a high frequency of hypogonadism in male patients with metabolic syndrome. Moreover, they suggest that insulin might be related to the findings of low SHBG, total and free testosterone levels, in this series of patients. We also highlight the importance of the precocious identification of hypogonadism in men with metabolic syndrome.

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