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Late-Onset Hypogonadism in Male Patients Over 60 Years of Age with Metabolic Syndrome

Altmış Yaş Üstü Metabolik Sendromlu Erkek Hastalarda Geç-Başlayan Hipogonadizm

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Abstract

Purpose: The aim of the study was to determine serum androgen levels and the frequency of late-onset hypogonadism (LOH) in patients over 60 years of age with metabolic syndrome (MS) and its correlation with parameters of MS.

Material and Method: Men over 60 years of age who were diagnosed with MS according to the Adult Treatment Panel III (ATP III) criteria in the internal medicine outpatient clinics at Cerrahpasa Medical School (n=30) and healthy controls (n=30) were included in the study. Total testosterone and sex hormone binding globulin (SHBG) levels were analysed. Bioavailable and free testosterone levels were calculated. The participants filled up the Beck Depression Inventory (BDI) and Aging Male Symptoms (AMS) questionnaire forms themselves without any help of the physician.

Results: LOH rates were 30% and 13.3% in the MS group and healthy control group, respectively (p=0.11). Serum total testosterone and SHBG levels were significantly lower in the MS group compared to controls (p=0.004 and p=0.003, respectively). A negative correlation was found between total testosterone and MS components. BDI and AMS questionnaire scores in the two groups were not significantly different.

Discussion: Serum total testosterone and SHBG levels were lower in the MS group, and inversely proportional to this, insulin resistance and intensity of MS components were increased. *Turk Jem 2013; 17: 22-7*

Key words: Metabolic syndrome, late onset hypogonadism, testosterone, insulin

Özet

Amaç: Bu çalışmada altmış yaş üstü metabolik sendromlu (MS) erkek hastalarda serum androjen seviyelerinin, geç başlayan hipogonadizm (GBH) sıklıklarının ve bunların metabolik sendrom bileşenleri ile korelasyonunun saptanması amaçlanmıştır.

Gereç ve Yöntem: Cerrahpaşa Tıp Fakültesi İç Hastalıkları polikliniklerine başvuran 60 yaş üstü erkeklerden ATP III kriterlerine göre MS tanısı alanlar (n=30) ve sağlıklı kişiler (n=30) çalışmaya alındı. Total testosteron ve SHBG düzeyleri bakıldı. Hesaplanan serbest testosteron ve bioavailable testosteron düzeyleri hesaplandı. Çalışmaya katılanlar Beck depresyon ölçeği ve AMS sorgulama formunu doktor yardımı olmaksızın doldurdu.

Bulgular: GBH sıklığı metabolik sendromlu grubunda ve sağlıklı kontrol grubunda sırasıyla %30, %13,3 bulundu (p=0,11). MS grubunda serum total testosteron (p=0,004) ve serum SHBG düzeyleri (p=0.003) anlamlı olarak düşük bulundu. Total testosteron ile MS bileşenleri arasında negatif ilişki saptandı. İki grup arasında Beck Depresyon ve AMS sorgulama skorları açısından anlamlı fark bulunmadı.

Tartışma: Metabolik sendrom grubunda serum total testosteron ve SHBG düzeylerinin azaldığı ve bu azalmayla ters orantılı olarak insülin direncinin ve metabolik sendrom bileşenlerinin şiddetinin arttığı saptandı. *Turk Jem 2013; 17: 22-7*

Anahtar kelimeler: Metabolik sendrom, geç başlayan hipogonadizm, testosteron, insülin

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Introduction

The metabolic syndrome (MS) involves a group of medical conditions which have multiple pathological components leading to the development of diabetes and cardiovascular disease (1). It is characterized by changes in carbohydrate metabolism, insulin resistance, obesity, increased waist circumference (WC), abdominal fat, hypertension, and dyslipidemia (2). Although MS has a complex pathogenesis and components, central obesity and insulin resistance have been considered in the etiology (3). The close association between hypogonadism and MS has been the focus of numerous studies (4). In men, testosterone deficiency may contribute to the development of MS (5). Longitudinal studies, the Massachusetts Male Aging Study (6) and the Baltimore Longitudinal Study of Aging (7), have confirmed that the prevalence of MS increases with age and that it is related to hypogonadism.

Several studies have demonstrated that low testosterone levels are associated with insulin resistance and high testosterone concentrations are connected with insulin sensitivity (8-10). The hyperinsulinemic state inherent in MS leads to inhibition of the hepatic production of sex 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 (11). Several theories have been proposed to explain the decrease in the testosterone levels, including reduced testicular vascularization, reduced response of the Leydig cells to the luteinizing hormone (LH), loss of expression rates and amplitudes of gonadotropins and alterations in SHBG levels and elevation of estrogen concentrations (12). Androgen deficiency in adults can cause sexual dysfunction, decrease in intellectual capacity, fatigue, depression, and osteoporosis (13).

Psychiatric symptoms associated with hypogonadism and depression are not easily distinguished. For example, low libido, fatigue, reduced self-esteem, and irritability are some of the common symptoms in both. Elderly hypogonadal men often suffer from affective disorder, depression, and cognitive deficiencies, which have been shown to be associated with testosterone deficiency in various studies (14-19).

Numerous questionnaires have been developed for objective evaluation of these patients and for their follow-up of the symptom improvement during therapy. Of these, the Aging Male Symptoms (AMS) questionnaire is accepted by both the International Society for the Study of the Aging Male (ISSAM) and the Turkish Society of Andrology. It is also found to be compatible with Turkish.

The aim of the study was to evaluate serum androgen levels and the frequency of late onset hypogonadism (LOH) in patients over 60 years of age with MS and its correlation with parameters of MS by using androgen deficiency symptoms based on AMS results and affective state of the patient based on BDI scores.

Material and Methods

Men over 60 years of age who were diagnosed with MS in the internal medicine outpatient clinics at Cerrahpasa Medical School (n=30) between June 2007 and January 2008 and healthy controls (n=30) were included in the study. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines as the presence of three or more of the following (20): 1) Men with WC greater than 102 cm 2) Serum triglyceride≤150 mg/dl 3) HDL cholesterol<40mg/dl 4) Blood pressure (BP) higher than 130/85mm/Hg, 5) Fasting Blood Glucose= 110-126 mg/dl.

Subjects with type 2 diabetes mellitus, active systematic diseases, urogenital malignancies, receiving antiandrogen or glucocorticoid treatment, and those with diagnosed depression or ≤receiving antidepressant treatment, primary gonadal insufficiency were not included in this study.

In our study, the diagnosis of LOH was based on the presence of symptoms, such as depression, erectile dysfunction, decrease in libido, lethargy, sleep and concentration disorders and total testosterone levels less than 200 ng/dl or total testosterone being 200-400 ng/dl but free testosterone less than 8.91 ng/dl (21).

All the patients were invited to the hospital by phone. The patients were enrolled into the study upon their informed consent. Blood pressure was measured in sitting position after a 5-minute rest, twice with a 3-minute interval, and the average measurements were recorded. Hip circumference (HC) and WC were measured then waist to hip ratio (WHR) was calculated. The height and weight were used to calculate the body mass index (BMI).

Depression was diagnosed by self-administered BDI (22). This test consists of 21 questions and aims to determine the severity of depression. The coexistence of depression was determined when the overall score was equal to or greater than 17. The BDI has been validated in the Turkish language and in Turkish population.

Androgen deficiency and its severity were measured using AMS questionnaire forms. The AMS questionnaire was also self-administered by the patients. It consists of 17 questions and each question is scored between 1 and 5. While a total score of 17-26 means that there are no symptoms; 27-36 means mild; 37-49, moderate, and over 50, severe symptoms. In the AMS, questions number 1, 2, 3, 4, 5, 9 and 10 are somatic while 6, 7, 8, 11 and 13, psychological. Questions number 12, 14, 15, 16, and 17 are designed to analyze sexual components.

The data on the levels of glycemia, insulin, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, albumin, and globulin were collected from the files of the patients. Insulin resistance was estimated from the homeostasis model assessment insulin resistance index (HOMA-R: fasting plasma glucose x fasting insulin level x 0.0551 / 22.5) (23).

Blood samples were obtained at 8:00- 10:00 AM after an overnight fast. The blood was immediately centrifuged at 4°C, and the serum was stored at -80°C until assay. Total testosterone, SHBG, and albumin levels were used to determine the levels of bioavailable testosterone and calculated free testosterone. Total testosterone and SHBG were measured with chemiluminescent enzyme immunoassay (ECLIA:electro-chemi-illuminescens immunoassay) kits from Abbott Architect IL 60064 (reference levels; SHBG=39.7 nmol/L (17.1-77.6), total testosterone=486 ng/dl (254-853)). All the biochemical tests were done in Cerrahpasa central laboratories. This study was approved by the Ethics Committee of Istanbul University Cerrahpasa Medical School .

The data were evaluated using SPSS version 13 for Windows. The groups were compared with Mann-Whitney U test as the distribution if variables were non-normal. Spearman correlation coefficient was used to assess the correlation. A p value of less than 0.05 was considered statistically significant. Chi-square test was used when necessary.

Results

General characteristics of the MS group and the control group are shown in Table 1. In our series, the frequency of LOH was 30% (9/30) in the MS group and 13.3% (4/30) in the healthy controls (p=0.11). In the MS group, serum total testosterone levels (p=0.004) and serum SHBG levels (p=0.003) were significantly lower than those in the control group. When the testosterone and SHBG levels adjusted for BMI before comparison among the groups, the significance disappeared. However, no differences were detected between the two groups for bioavailable testosterone (p=0.29) and calculated free testosterone (p=0.25) levels (Table 2). Moreover, there was no statistically significant difference in BDI scores and AMS questionnaire scores between the two groups (Table 3).

No significant correlation was determined between age and total testosterone in Spearman correlation analysis. However, age significantly negatively correlated with bioavailable testosterone (p<0.01, r=-0.45) and calculated free testosterone (p=0.001, r = -0.43), while a strong positive correlation was determined between SHBG and age (p<0.01, r=0.45).

In the evaluation of the relationship of MS components with serum testosterone levels, total testosterone moderately negatively correlated with systolic blood pressure (p=0.01, r=-0.31), diastolic blood pressure (p=0.01, r=-0.31), BMI (p=0.02, r=-0.29), insulin (p=0.03, r= -0.27), total cholesterol (p=0.03, r=-0.27), triglyceride (p=0.01, r=-0.30), and LDL cholesterol (p=0.01, r=-0.32). There were a negative correlation between total testosterone and HOMA-R values

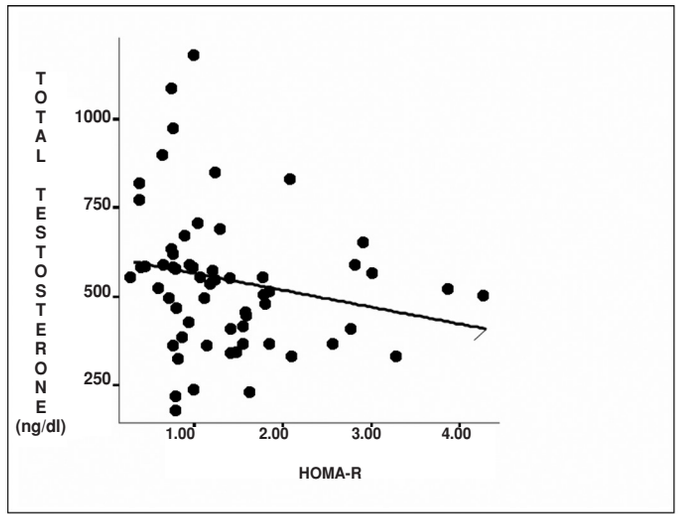

Figure 1. Negative corelation was shown between total testosterone ve HOMA-R values.

Table 1. The general characteristics of metabolic syndrome and healthy control grup

	Healthy control (n = 30)		Metabolic syndrome (n = 30)		p
	median	IQR	median	IQR	
Age	74	62-80	69	65-76	0.81
SBP	120	110-130	150	140-170	<0.001
DBP	75	60-80	90	80-91.25	<0.001
Height	170	165-172	167.5	163-173	0.32
Weight	68.5	61.75-77.25	82	77-88	<0.001
BMI	24.25	23.24-26.5	28.8	27.47-30.55	<0.001
Waist circumference	94	85.75-98	109	106-112.5	<0.001
Hip circumference	96	91-101.25	107.5	103.75-112.25	<0.001
Waist- hip-ratio	0.95	0.92- 0.98	1.01	0.99-1.03	<0.001
Fasting blood glucose	92	86-99.5	105.5	92.75-113.25	<0.001
Total cholesterol	182.5	155.5-200.5	199.5	169.25-230.75	0.07
Trigliceride	88	72.2-115.75	157	120.5-181.25	<0.001
HDL cholesterol	48.5	41.75-57.25	39	37-46	<0.001
LDL cholesterol	117	89.75-134.5	132	104.75-147.25	0.10
HOMA-R	1.17	0.80-1.77	1.60	1.01-2.66	<0.001
Insulin	4.31	3.19-5.59	6.46	4.85-10.02	<0.001

IQR: Interquartile range, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, HOMA-R: Homeostasis Model Assessment Insulin Resistance Index

(p=0.01, r=-0.32) (Figure 1). Total testosterone was strongly negatively correlated with WC (p=0.007, r=-0.34) and HC (p=0.004, r=-0.36). Similarly, MS components did not statistically significant correlated with bioavailable testosterone and calculated testosterone.

When SHBG was compared with the MS components, SHBG was strongly negatively correlated with BMI (p=0.003, r=-0.37), total cholesterol (p=0.007, r=-0.34), triglyceride (p=0.002, r=-0.39) and HOMA-R (p=0.005, r=-0.35). SHBG was also moderately negatively correlated with weight (p=0.02, r=-0.28), WC (p=0.03, r=-0.28), HC (p=0.01, r=-0.19), and insulin (p=0.01, r=-0.31).

MS components did not significantly correlated with BDI scores, AMS-total scores and age. As expected, AMS-total scores significantly positively correlated with AMS subtypes and BDI scores (p<0.01, r=0.49). AMS-sexual moderately positively correlated with age (p=0.04, r=0.25) and WHR (p=0.04, r=0.26), however, moderately negatively correlated with bioavailable testosterone (p=0.04, r=-0.25).

Discussion

In this study, we have shown that the frequency of LOH was increased in patients with MS than in healthy controls, but the difference was not statistically significant. In the MS group, serum total testosterone levels and serum SHBG levels were significantly lower than those in the healthy controls, inversely proportional to this, insulin resistance and intensity of MS components were increased.

When all cases were evaluated, LOH was diagnosed in 13 of 60 patients. In the Baltimore Longitudinal Study of Aging, total testosterone levels were evaluated in the age groups over 60, 70, and 80, and the incidence rates of biochemical hypogonadism were 19%, 28%, and 49%, respectively (24). In the Massachusetts Male Aging Study, the crude incidence rate of androgen deficiency was 12.3 per 1,000 person-years, and the rate increased significantly with age (21). Recently, Tajar A et al. (25) reported that LOH incidence was 2.1% in subjects aged 40-79 years. LOH was defined as the presence of three sexual symptoms (decreased frequency of morning erections and sexual thoughts and erectile dysfunction) in combination with total testosterone less than 11 nmol/L and free testosterone less than 220pmol/L. In the literature, there are important differences in LOH and androgen deficiency definitions, as well as in cut-off values for total and free testosterone levels. Although hypogonadism was found twice more in patients with MS than in healthy controls, it was not statistically different in our study. The limited number of the patients can be the reason for this. Corona et al. (26) in their study on 1134 males with a mean age of 52, determined LOH prevalence rate of 29% in patients with MS diagnosed with ATP III criteria and 13.2% in healthy controls.

Although age, geography, ethnicity, and lifestyle issues are related to MS, hypogonadism also has been shown to have a strong relationship with MS. Kupelian et al. (6) showed that low total testosterone and low SHBG levels were risk factors for MS, even when they restricted the association to men with asymptomatic androgen deficiency. Similar to our results, a study by Kaplan et al. (27) performed on 864 male subjects with a mean age of 52 showed that patients with MS had lower levels of serum total testosterone than healthy controls. The MS parameters which

Table 2. Serum testosterone and SHBG levels of metabolic syndrome and healthy control grup

	Healthy control (n=30)		Metabolic syndrome (n=30)		p
	median	IQR	median	IQR	
Total testosterone	589	520.5-687.5	460	371.5-567.25	0.004
Bioavailable testosterone	198.5	129.25-224	173	135.25-201	0.29
SHBG	65.5	52.28-90.15	49.5	38.65-62.33	0.003
Calculated free testosterone	8.68	6.28-10.02	7.29	6.02-8.93	0.25

IQR:Interquartile range, SHBG= Sex hormone binding globulin

Table 3. Beck Depresion Scale and AMS Questionnaire form puans of metabolic syndrome and healthy control grup

	Healthy control (n=30)		Metabolic syndrome (n=30)		p
	median	IQR	median	IQR	
Beck depression scale	10.5	6-14.25	8	5.75-13	0.28
AMS - total	33	29.75-41	32	29-38.5	0.53
AMS - somatic	13	10-19.5	13	11-18	0.84
AMS - physocologic	9	7.75-12	8	6-11	0.10
AMS - sexual	11.5	9-15	11	10-13	0.84

IQR:Interquartile range

had the strongest correlation with low testosterone were FBG, TG and obesity. Laaksonen et al. (28) reported that free testosterone and SHBG levels were decreased by 11% and 18%, respectively in subjects with MS compared to those without MS. However, SHBG and total testosterone levels were negatively correlated with fasting insulin and glucose levels.

Visceral obesity is strongly related especially to MS and insulin resistance, and negatively associated with testosterone levels (29). In a meta-analysis of more than 300.000 subjects, Bogers et al. (30) showed, that obesity was an independent risk factor for MS. Osuna et al. (31) found lower total testosterone and SHBG levels in obese subjects with high BMI. They have concluded that with increasing BMI and insulin resistance, total testosterone and SHBG levels reduce. In a clinical study, Mulligan et al. (32) showed a negative correlation between obesity and testosterone levels. We observed a negative correlation of total testosterone levels with BMI and WC in patients with MS. Svartberg et al. (33,34) found that increasing WC predicted low testosterone levels. They also suggested that WC was better at predicting testosterone levels than was BMI.

In our study, total testosterone levels negatively correlated with levels of insulin and HOMA-R. Oral glucose tolerance test was not performed; this is a limiting factor in this study. Muller et al. (35) showed that high total testosterone and SHBG levels were associated with high sensitivity of insulin and reduced risk of MS onset, independent from blood insulin levels and antropometric measurements of the body. They have also determined that these hormones had protective effects against MS development. Caldas et al. (36) reported an increase in both insulin resistance index (HOMA-R) and index that measures pancreatic beta cell function (HOMA-β) in hypogonadic patients with MS.

We also found significantly lower SHBG levels in patients with MS and inverse correlation of SHBG with insulin, HOMA-R, BMI, WC. Previously, low SHBG levels were described in individuals with MS and were associated with insulin resistance, carbohydrate intolerance and central obesity (37). It has been suggested that SHBG levels could be used as a specific marker of insulin resistance as well as one of the components of the MS (38).

A few randomized clinical trials have evaluated the effect of testosterone replacement treatment (TRT) in patients with MS. Recently, a meta-analysis reported that in patients with MS, TRT was associated with a significant reduction of fasting plasma glucose, HOMA-R, triglycerides and WC, as well as with an increase of HDL-cholesterol (39).

In this study, based on the results of AMS questionnaire, no statistically significant differences were found in scores between the group with MS and healthy controls and between those with LOH and without LOH. However, AMS-sexual scores moderately positively correlated with age and WHR, while a moderately negative correlation was determined between AMS-sexual scores and bioavailable testosterone. Esposito et al. (40) reported reduced sexual functions in obese individuals. Schiavi et al. (41) have showed that sexual desire reduces, when the bioavailable testosterone levels decrease. Nevertheless, Basar et al. (42) found negative correlations between AMS–sexual score and androgen levels. On the other hand, Miwa Y et al. (43) have emphasized that androgen deficiency symptoms and serum testosterone level are not correlated, and AMS is not successful enough for predicting biochemical hypogonadism. Multihormonal and complex mechanisms as well as serum testosterone levels in the development of androgen deficiency symptoms and different numbers and sociocultural levels of the subjects that have answered the questionnaires may all be the cause of the different results in the literature.

There were evidence with various results of the association between MS and depression. Skilton et al. (16) have found a correlation between MS and frequency of depression in both males and females. On the other hand, Herva et al. (17) have determined no correlation between MS and frequency of depression. In a study by Timonenores (18), there was a positive correlation between BDI scores and insulin resistance. In a review of the studies about the association between hypogonadism and depression in old males, it was emphasized that testosterone deficiency can contribute the persistent depression in older males and that some hypogonodal individuals with depression may benefit from testosterone replacement treatment, however, further studies may be helpful because the issue was not thoroughly illuminated (19). In a study by Rancho Bernardo (15), a statistically significantly negative correlation was found between BDI scores and bioavailable testosterone levels in older males with hypogonadism. The differences in the number of cases, depression scales which are used, and the criteria used to diagnose MS may be responsible for the discrepancies between the results of these studies as well as between the results of our study and the other studies in the literature.

In conclusion, the frequency of LOH was increased in patients with MS compared to that in healthy controls, but the difference was not significant because of the small number of patients. Nevertheless, serum total testosterone and SHBG levels were lower in the MS group than in healthy controls and inversely proportional to this, insulin resistance and intensity of MS components were increased. Increased WHR and reduced bioavailable testosterone levels may affect sexual functions.

Author Disclosure Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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