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TESTOSTERONE AND METABOLIC SYNDROME

Loreta BIÇA,
Mimoza LEZHA,
Neki KUKA

University Hospital Sh. Ndroqi, Tirana, Albania
University Hospital Center Mother Theresa, Department of Cardiology & Cardiac Surgery, Tirana, Albania

Abstract

Obesity, diabetes, hypertension, dyslipidemia, components of the metabolic syndrome (MS) is more common in men with lower testosterone levels. We have studied the relationship between endogenous sex hormones and metabolic syndrome in 933 men (27-72) with suggestive symptoms of CAD (coronary artery disease) in a cross-sectional study. The patients perform diagnostic and/or PTCI angiography.

Results: In total the group received the study, the prevalence of diabetes was 17%, arterial hypertension (HBP) was 54%, the low level of HDL was in 75%, and hypertriglyceridemia was in 52% of patients. Obesity (BMI is assessed in 518 patients) was 38% of patients. The prevalence of metabolic syndrome was 11%. The prevalence of metabolic syndrome was higher in men with CAD (12.75%) compared to the control group without CAD (6.15%) p = 0.0003. Patients with MS have lower levels of testosterone compared to patients without MS, regardless of the presence or not of CAD P <0.0001.

Conclusion: Metabolic syndrome in men is associated to lower levels of testosterone. On the other hand, the metabolic syndrome is more common in patients with CAD compared to normal. MS is positively associated to the extent of CAD.

Introduction

Cardiovascular diseases are the most common cause of morbidity and mortality in the Western world today. Metabolic syndrome is associated with increased atherosclerotic cardiovascular morbidity .On the other hand men have risk for developing SAK earlier than women, this bias occasionally attributed androgen. Metabolic syndrome was described for the first time in 1923 (Kylin a Swedish physicist) as a clinical asossacion HTA and Gout (1). In 1988 Reaven described syndrome X as a constellation of insulin resistance, hyperglycemic, hypertension, HDLC reduction, increased triglycerides, and VLDL increase (2). Since that time, the concept of metabolic syndrome has evolved and is considered a risk factor for CAD.

International Diabetes Federation, National Heart Lung Blood Institute (NHLBI), Word Heart Federation, International Atherosclerosis Society, American Heart Association in a joint statement have defined specific criteria metabolic syndrome: (3) Patient to meet 3 of the following 5 criteria: waist circumference growth, hypertriglyceridemia, Reduction of HDLC, HTA, impaired glucose tolerance and / or diabetes, are considered to have metabolic syndrome(4).

Some of the major cardiovascular risk factors in men, as hyperinsulinemia, Hyperglycemia, hypertension, hypercholesterolemia, hypertriglyceridemia, decreased levels of HDL, smoking, and obesity, often accompany each other (5). The interplay between these factors that suggest the presence of a common underlying factor may be related to sexual hormonal modification (6).

Testosterone

It is a hormone steroid - androgens group. Testosterone mainly secreted in the testes of males and the ovaries of females. A very small amount is secreted by glands suprarenal. Testosterone is the male sex hormone and anabolic steroids. Average adult male's plasma testosterone concentration is 7-8 times higher than in women in the same age group (7).

Largest concentration of T in the blood is in the early hours of the morning, and falls during the day (8). Significant decreases T serial level recorded over the age of 50 years (9), this is called andropausa, is similar to reducing estrogen, menopause among women, but without signs and symptoms similar.

In America T levels in men below 300 ng/dl (estimated from blood samples taken in the morning) are considered low, hypo testosterone (10).

Observational studies have suggested that the fall of T with age may not be inherent with aging. Testosterone

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falls gradually with age in men amounting to 0.4-2.6% on year (9).

The factors responsible for the decline in the level of T with age are not well defined - linked to cell dysfunction, reduction function hypothalamus pituitary axis. Also, other factors and behaviors that contribute to this decrease (11-13) are the T levels of obesity, alcohol, and psychological stress (14).

Metabolic effects of testosterone

Some evidence suggests that testosterone causes modeling metabolic risk factors such as diabetes, insulin resistance (15), obesity (16) hypercholesterolemia (17,18) and hyper triglycerides (18).

Recently are a number of reviews that clearly identify the important connection between hypo gonad, metabolic syndrome, diabetes and CAD (19,20,24).

There is convincing evidence that lowering of testosterone level is an independent risk factor for the development of metabolic syndrome and type II diabetes in men. On the other hand is accumulated evidence that lower levels of T are a risk factor for CAD (25).

Metabolic syndrome is associated with significant increase in cardiovascular morbidity and mortality. On the other hand there is significant evidence that the greater prevalence of metabolic syndrome in men with hypo testosterone (26).

Basic mechanisms of connectivity between the levels of T and CAD are not clear completely. But it is assumed that the reduced levels of T are associated with adverse levels of risk cardiovascular as: lipids, blood pressure, which are components of metabolic syndrome. There are few data on the relationship of testosterone levels with metabolic syndrome

The aim of our study was to evaluate the correlation of testosterone levels with metabolic syndrome according to National Cholesterol Education Program (NCEPT) in men.

Material and Methods

Were included in the study 933 men with an average age 56 ± 8.2 (27-74) admitted to the University Hospital Center Mother Theresa department cardiology our subjects had data suggestive of coronary artery diseases (CAD) and undergoing diagnostic *angiography* and/ or revascularization. In the patients evaluated CAD risk factors, in particular glycemia fasting lipid profile, the presence or not of HTA. In this group became the assessment of BMI reference measurement of height and body weight with the classical method. During the examination, the weight and length were measured in standing position without shoes with light clothes. BMI (Index of body mass) was calculated as the ratio of weight in kilograms to the square of the length in meter. On the morning of the day of the performance, *angiography* (at 8-9) took biochemical tests, and blood samples to determine the level of testosterone. Testosterone level analysis method became radioimmunoassay.

Were excluded from the study patients with androgen treatment, prostate cancer and/or deprives therapy for prostate cancer, hypogonad primary, acute myocardial infarction, heart valve disease.

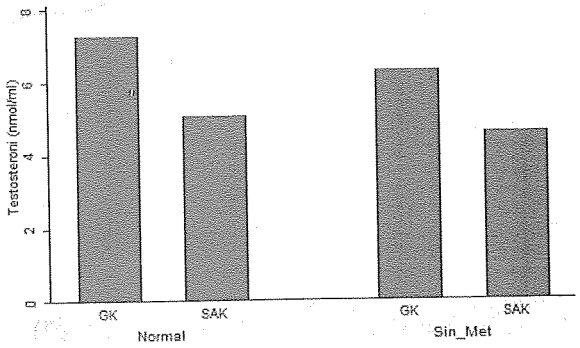
To determine patients with metabolic syndrome (MS) regardless of the presence or not of CAD is used ncept criteria (1): MS is defined as present when three or more of the following criteria: plasma glucose levels less than 6.1 mmol/liter (110 mg/dl), triglycerides less than 1.7 mmol/l (150 mg/dl), HDL cholesterol less than 1.0 mmol/l (40 mg/dl), blood pressure (BP) less than 130/85 mm Hg, waist circumference more than 102 cm. During the study, we did not measure the circumference, but are referred to BMI (over 29kg/m^2 = obesity).

In this way, patients were divided in 2 groups: group with metabolic syndrome (103) and the group without MS (830).

Statistical analysis

Continuous variables (age, cholesterol, triglyceride, etc). There are present as average values ± standard deviations. We used using the "t" of the student test In order to check the hypothesis that the differences between the two groups in terms of various parameters are statistically significant or not. As for the comparison of categorical variables (presence or not of diabetes, hypertension), are using frequency tables and Pirsonit criterion $\chi 2$. In all tests, the differences between the two groups were considered statistically significant for $p \leq 0.05$ significance level.

Patients who suffer from metabolic syndrome characterized by reduced levels of testosterone, with about 0.82 nmol/ml. Difference is statistically significant with significance level P <0.0001, and is noted as a healthy group and in the group of patients with CAD (Figure nr.1).



There is an association statistically significant (P <0.002) between the presence of metabolic syndrome and number of vessels coronary with significant

stenossis. Prevalence of metabolic syndrome patients varies from 6.15% in group of patients without coronary artery disease (CAD), 11.1% in the group of one vessel disease, 9.1% in the group of two vessels disease, and 16.2% in the group with three vessels disease. In total, the prevalence of patients with metabolic syndrome was 12.77% in the group with CAD, and 6.15% in the control group. The difference is statistically significant, with significance level P=0.0003.

There is a slight correlation (r = -0.14), but statistically significant (P = 0.0299) between testosterone levels and body mass index. With increasing BMI, the level of testosterone undergoes a slight decrease (Table nr.1).

It was studied the links between level testosterone with cholesterol, HDL, LDL, triglycerides, in the whole group of patients in study (Table nr.2).

As seen from Table nr.2, the testosterone level is not related to cholesterol and LDL-c values. But, there is a positive correlation between the testosterone level and HDL-c, and a negative correlation between testosterone and triglyceride.

There is a strong correlation (P <0.002) between testosterone levels and the presence of diabetes. In diabetic patients the testosterone level is 4.904 nmol / ml, versus 5.706 nmol / ml in the control group (Table nr.3). Thus, patients with diabetes are characterized by testosterone levels 0.80 nmol/ml lower than control group.

Testosterone levels decrease by about 0.36 nmol / ml in the group of patients suffering from hypertension,

There is an association statistically significant (P <0.002) between the presence of metabolic syndrome and number of affected vessel

In the metabolic syndrome patients, 45% of the cases had three vessel diseases.

Table nr.1. Testosterone levels (nmol/ml) according to body mass index

Class BMI	Average value of testosterone level (nmol/ml)	Nr. of patients
Normal	5.531±1.825	105
Overweight	5.554±1.877	216
Obese	5.097±1.894	197
Total	5.376±1.882	518

Table nr.2 .Testosterone levels and lipid

Lipids	Lipid level ng/dl	Number of patients	The average value of T (nmol/ml /ml)	Interval of 95% confidence	Difference
Cholesterol	≤ 220	703	5.577	5.420 – 5.734	0.036 P=0.820
	> 220	230	5.541	5.270 – 5.811	P=0.820
HDL.c	≥40	231	5.804	5.567 – 5.957	0.358 P=0.0500
	< 40	702	5.490	5.506 – 6.102	P=0.0500
LDL.c	< 150	723	5.600	5.367 – 5.675	0.140 P=0.1990
	> 150	210	5.460	5.197 – 5.722	P=0.1990
Triglyceride	< 150	442	5.792	5.582 – 6.003	0.069 P=0.0010
	> 150	491	5.366	5.193 – 5.539	P=0.0010

Table nr.3. The level of testosterone in pt. with hypertension, diabetes and metabolic syndrome

Disease	yes/no	Number of patients	The average value (nmol /ml)	Interval of 95% confidence	Differences
Diabetes	no	772	5.706	5.556 – 5.857	0.802
	yes	161	4.904	4.613 – 5.196	P=0000
Hypertension	no	428	5.762	5.567 – 5.957	0.358
	yes	505	5.404	5.216 – 5.591	P=0.0048
Metabolic syndrome	no	830	5.658	5.514 – 5.803	0.816
	yes	103	4.842	4.476 – 5.208	P=0.0001

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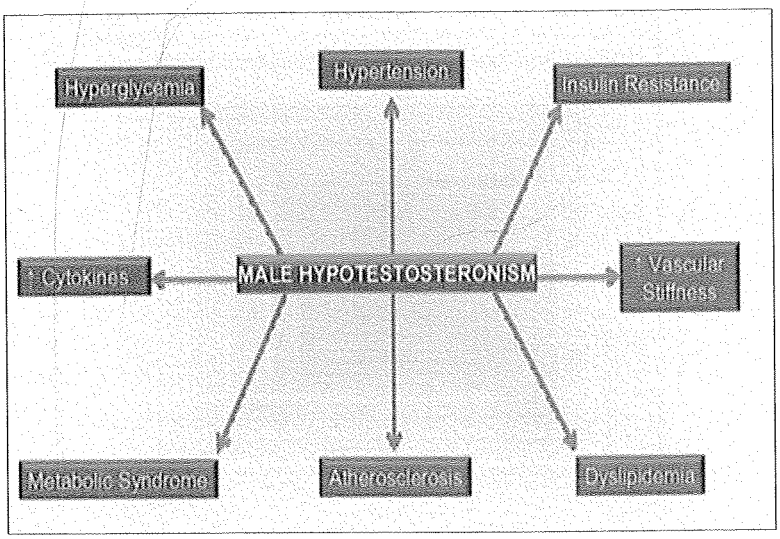
Discussion

This study cross-sectional in men with age (27-74) showed that: Men with metabolic syndrome (MS) have significant reduced the average levels of testosterone (4.84 nmol/ml) compared with normal subjects (5.65nmol/ml) without MS ($p < 0.001$).

There are a number of epidemiological studies that identify the correlation of testosterone with metabolic syndrome. In the "Finish study" (1896) in which were included non-diabetic men, followed-up for 11 years, reported that T levels were reduced significant in those with the metabolic syndrome compared with normal subjects (27) and that men with metabolic syndrome have an increased risk for hypo gonadism (27). Another study that included 803 men showed that hypo gonadism was frequent in those with metabolic syndrome (28). Very important data coming from large study massachuster Male Aging Study included 950 men without metabolic syndrome and not obese who had reduced levels of T. From this study it was concluded that hypo-testosterone had predictive value in late development MS (29).

Association between reduced levels of T and SM, is in accordance of a series of observational studies of testosterone and cardiovascular risk factors (11,30,31,32,33,34,35). Low levels rather than higher levels of testosterone in men are associated with a range of cardiovascular risk factors: lipid profiling atherogenic insulin resistance, obesity and profile fibrinolytic protrombotik (36) (Figure nr.1).



Testosterone and obesity. On the analysis made in the group, which was, estimated BMI (total 518 subjects) resulted: A slight negative correlation, but statistically significant between testosterone levels and BMI ($r = -0.14$, $p = 0.0299$). Therefore, testosterone level is in inverse correlation with BMI. The population is limited and apparently, until now obesity is probably not very strong risk factor for CAD in Albanian men.

There is a strong inverse correlation between the deposition of adipose tissue visceral and testosterone level in men. Viscera obesity in men is usually associated with reduced levels of testosterone (37). Central deposit of fat is associated with increased activity aromatizes which converts the periphery testosterone in estrogen (38). On the other hand androgen deficit reduces lipolise and is responsible for obesity (39). Men with hypo-testosterone have increased adipose visceral tissue (40).

Testosterone, Insulin Resistance and diabetes. In our study was proved that diabetes mellitus was a risk factor for CV disease. Diabetes was present in 20% of men in the diseased group, and 9.4% in the healthy ($p < 0.001$). By logistic regression analysis we concluded that diabetics have the opportunity, the likelihood of suffering from CAD 2.34 times more than non-diabetics. Another important finding was the inverse correlation between testosterone levels and diabetes in patients with or without CAD. In diabetics average testosterone level was 4.9 nmol/ml in non-diabetic subjects average testosterone was 5.7nmol/ml ($p < 0.002$).

Diabetics, according to our data have testosterone levels averaged 0.80 nmol lower than non-diabetics do. Resistance to insulin and Hyperglycemia are key features of type II diabetes. There are evidence that: Reduced levels of T are associated with diabetes. In a study of 1292 healthy non-diabetic men inverse correlation was found between T and insulin levels, independent of age and obesity (41). In a metanalisse of 21 clinical reports which were included data from 3835 men confirmed: that there is a high prevalence of reduced levels of T in men with diabetes and /or metabolic syndrome (42).

A number of longitudinal studies have shown that low testosterone levels are an independent factor for the development of diabetes and SM (26).

Dyslipidemia and Testosterone in MS. In the total group of subjects (933), with or without CAD we evaluated the correlation of testosterone levels and lipid profile. We found no link between testosterone levels and cholesterol and LDL-c cholesterol. However, it seems clear: inverse correlation between testosterone levels and the level of triglycerides (TG) ($p < 0.001$).We also found a positive correlation between testosterone level and HDL-c (p, 0.05), in men with and without coronary artery disease. Apparently sexual hormones have a specific gender effect on risk factors. It appears from our study that reduced levels of testosterone are associated with reduced levels of HDL c, and increases level of TG. At the same time highlighted a negative correlation between HDL and triglycerides (r = -0105, p, 0.0193). HDLC and triglyceride levels are two main components of Metabolic Syndromes, while not included LDL c and cholesterol. Increased TG and cholesterol are risk factors for cardiovascular events confirmed, while the HDLC has protective effect against atherosclerosis. Studies have shown that reduced levels of HDL-c are associated with increased CV risk. HDL-c presents a complicated picture and the effect seems to be specifically linked to the (gender) 43 Decreased levels of HDL related with CHD more in men than in women (44). Testosterone level correlates positively with the level of HDL-c in healthy men and diabetics (45,46). A limited number of studies have found a negative correlation between the level of T and LDL-C and cholesterol (32).

Our data confirm a positive correlation between testosterone level and HDL-c level.

Testosterone and hypertension (HBP). From our data, result that the HBP patients had levels of testosterone 0.36 nmol / ml lower than those that without the HBP. Studies on the correlation between testosterone and hypertension are conflicting.

In a cross sectional study found inverse correlation between systolic pressure, diastolic and testosterone level. Men with reduced levels of testosterone have (hypertension) HBP (19). In another study was reported that the prevalence of hypertension is higher among men than among women (47). Mechanisms responsible for this gender difference are still unknown, but androgens seem to have a potential role in humans and animals. After puberty, it is noticed that boys have higher pressure than girls do in the same age group (48). For this reason, the male sexual hormones-testosterone has been implicated in the etio -pathogenesis of hypertension.

High incidence of HBP and CAD in men compared to women partially is associated with gender differences in tone of blood vessels. This attributed to the relaxing action, endothelium dependent testosterone in the blood vessels and inhibitory action on the smooth muscles of blood vessels (49). On the other hand it was reported that testosterone plays a role deposits adipose tissue viscera (50). In this way, the connection of lower testosterone level with HBP thought to be mediated by obesity (51).

As mentioned above hypo testosteronemia closely is associated with metabolic syndrome. Metabolic syndrome is a group of cardiovascular risk factors. When three of the five key components that define metabolic syndrome are present, clinical trials show that cardiovascular disease is present at least in its initial form. Our data evidenced that the prevalence of metabolic syndromes was significant higher in the men with CAD compared to controls without CAD (12.7% / 6.1% P = 0.0003). The prevalence of metabolic syndromes correlates positively with the gravity of the CAD. In our study metabolic syndrome was present 11.1% at the patients with one vessel disease,16.2% in the patients with three vessels disease. Metabolic syndrome is a constellation cardiovascular risk factor and the mechanisms are obviously related to each component.

Conclusion

Metabolic syndrome in men is associated with reduced levels of testosterone. Many of the components of MS (obesity, diabetes, HTA, the increased level of triglycerides) correlate negatively with testosterone level. While HDL-c level correlate positively with hypo testosterone. On the other metabolic syndrome is more prevalent in patients with CAD and correlates positively with the gravity of the CAD.

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