



## **The Hypothalamo-Pituitary-Gonadal System in Men with Ischemic Heart Disease**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors ABHA and FJ is designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FJ and SZ managed the analyses of the study. Author LW managed the literature searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Purpose:** This Research was to study the functional state of the hypothalamic-pituitary gland-gonadal system in males with Ischemic Heart Disease (IHD), as well as the effect of hormonal correction of the revealed disorders on factors of pathogenesis and the course of IHD.

**Materials and Methods:** We examined 120 males with IHD of different severity of disease, aged 20-50 years and 34 healthy males of the same age with normal body weight and with uncompromised history for diseases of the endocrine system. Among those surveyed were not included alcoholou anabolizant steroids abusers with severe somatic and inflammatory diseases of the genital organs (prostatitis, urethritis, orchitis). The body weight of patients fluctuated within  $\pm 10\%$  of the ideal. At the time of the examination, all the patients were married, 2 were divorced, and all had children.

Depending on the age, the examinees were divided into 2 groups: the first - 44 patients in the age of 20-35 years, the second - 76 patients 36-50 years old.

The patient was examined in Ashgabat city, Hospital with the Scientific- clinical Center of Cardiology (Turkmenistan).

**Results:** In the I age group, 8 patients had post infarction cardiosclerosis, in which there was a

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slight decrease in sexual activity, in others - angina pectoris of different functional classes (there was no violation of sexual activity).

The average content of T in the fasting serum of males with IHD of I group was significantly lowered, were noted a statistically unreliable tendency to increase of FSH and a statistically significant increase in the LH/T ratio. The mean levels of LH, PRL and E<sub>2</sub> did not differ from the corresponding indices in healthy individuals.

**Conclusion:** Patients with IHD have decreased testosterone secretion, especially at a young age.

*Keywords: Hypothalamic-pituitary gland-gonadal system; ischemic heart disease.*

## 1. INTRODUCTION

It is known that gonadal hormones have a pronounced effect on lipid metabolism, the condition of the arterial wall (especially its permeability), and the coagulogram parameters [1]. In general, most researchers pay more attention to the protection of estrogen and less attention to the effect of androgen when studying the gender differences of cardiovascular system. Recent clinical and animal studies have shown that androgen also plays an important role in the development of cardiovascular diseases [2,3].

Androgens have a distinct effect on the metabolism in the myocardium: they help increase the contractile elements, accumulate energy substances, and have a coronarolytic effect. According to some authors, there is a direct correlation between the degree of manifestation of coronary atherosclerosis and a decrease in the function of the gonadal glands in males [4].

Gender differences in cardiovascular disease are at least partly thought to be mediated by sex hormones and their receptors. The incidence of myocardial hypertrophy in male was significantly higher than that in premenopausal female, but this difference disappeared in female postmenopausal women. Androgen was considered to promote myocardial hypertrophy, while estrogen was thought to inhibit can by activating PI3K pathway, thus protecting cardiomyocytes from myocardial hypertrophy. On the other hand, the increase of androgen level can also directly promote myocardial hypertrophy in male mice by changing calcium concentration [5]. However, the literature data on the state of the hormonal system of the hypothalamus-pituitary gland-gonadal system in IHD are few and contradictory.

Recently, there are also related articles reporting that sex hormone levels may help predict cardiac arrest. A report published in Heart Rhythm

showed that sex hormone levels help identify people at increased risk of heart attack [6]. Previous studies have found that sex hormones have many important effects on the pathophysiology of cardiovascular diseases. Researchers from Cidas Sinai Heart Research Institute have found that men who experience cardiac arrest have lower testosterone levels, while men and women have estradiol. Dr. Sumeet Chugh of the Sinai Heart Research Institute said, "Since cardiac arrest is usually fatal, we are always looking for ways to predict patients who are prone to disease, so that we can focus on prevention. If we wait until the patient has a cardiac arrest before treatment, usually it's too late".

Participating patients in this study are from the ongoing Oregon Sudden Accidental Death Study. The researchers included 149 patients (median age 64.1 years; male 73.2%) who had experienced cardiac arrest and 149 matched control patients (median age 64.2 years; male 72.5%). The patient's testosterone and estradiol levels are based on blood samples taken during a heart attack or routine follow-up.

The study found that compared with the control group, the median testosterone level of men who experienced cardiac arrest was significantly lower (4.4 ng/mL VS 5.4 ng/m; P=.01), while men who experienced cardiac arrest (68 pg/mL VS 52 pg/mL; P<.001) and women ((54 pg/mL VS 36 pg/mL; P<.001) have lower estradiol levels.

After further multivariate analysis, it was found that higher levels of testosterone were only related to the decreased risk of cardiac arrest in men (OR=0.75; 95% CI, 1.9-6.4); higher levels of estradiol were associated with men (OR=2; 95% CI, 1.5-2.6) and women (OR=3.5; 95% CI, 1.9-6.4) were associated with increased risk of cardiac arrest. In men, a higher testosterone/estradiol ratio was associated with a decreased risk of cardiac arrest (OR=0.5; 95% CI, 0.4-0.7).

Chugh said: "We have reported for the first time that sex hormone levels are related to cardiac arrest, but these findings need further research. Higher levels of testosterone may prevent cardiac arrest in men, while lower levels of estrogen Alcohol may protect both men and women. This study analyzed 120 male IHD patients with different courses and 34 healthy men to explore the functional status of the hypothalamic-pituitary gland-gonad system in male IHD patients and the influence of hormone correction on the pathogenesis and course of IHD.

### 1.1 Purpose

This study was to study the functional state of the hypothalamic-pituitary gland-gonadal system in males with IHD, as well as the effect of hormonal correction of the revealed disorders on factors of pathogenesis and the course of IHD.

In consideration of that with age decreases the level of total and especially free testosterone, the study of this problem is advisable at the age of 20-50 years.

## 2. MATERIALS AND METHODS

We examined 120 males with IHD of different severity of disease, aged 20-50 years and 34 healthy males of the same age with normal body weight and with uncompromised history for diseases of the endocrine system. Among those surveyed were not included alcohol abusers with severe somatic and inflammatory diseases of the genital organs (prostatitis, urethritis, orchitis). The body weight of patients fluctuated within  $\pm 10\%$  of the ideal. At the time of the examination, all the patients were married, 2 were divorced, and all had children.

Depending on the age, the examinees were divided into 2 groups: the first - 44 patients in the age of 20-35 years, the second - 76 patients 36-50 years old.

The patient was examined in Ashgabat city, Hospital with the Scientific- clinical Center of Cardiology (Turkmenistan).

All patients underwent general clinical, endocrinological and urological examinations. To assess the sexual formula of males used a questionnaire scale recommended by the World Health Organization.

To exclude pathology of the pituitary gland, was carried out X-ray of the Turkish saddle, in a part of the patients - a computed tomography, to exclude diabetes was used test for tolerance to glucose (TTG).

Determination of fasting blood serum lutropin (LH), follitropin (FSH), prolactin (PRL), testosterone (T) and estradiol ( $E_2$ ) of patients were performed by radioimmunoassay methods by using of standard kits. Functional test of testicles (FTT) with gonadoliberin and single intramuscular injection of chorionic gonadotropin (CG) at a dose of 2000 units per  $1m^2$  of the body surface were made to all patients, followed by determination of serum concentration of T and  $E_2$  after 24 and 48 hours.

The diagnosis of IHD based on the clinical picture was also confirmed by electrocardiography, bicycle ergometry, 24-hour monitoring, echocardiography on the device of Toshiba (Japan), and X-ray coronary angiography by apparatus of Siemens (FRG).

## 3. RESULTS AND DISCUSSION

In the I age group, 8 patients had post infarction atherosclerosis, in which there was a slight decrease in sexual activity, in others - angina pectoris of different functional classes (there was no violation of sexual activity).

The average content of T in the fasting serum of males with IHD of I group was significantly lowered, were noted a statistically unreliable tendency to increase of FSH and a statistically significant increase in the LH/T ratio. The mean levels of LH, PRL and  $E_2$  did not differ from the corresponding indices in healthy individuals (Table 1).

In group II, 32 patients had post infarction atherosclerosis with impaired sexual function; in 8 - unstable angina; in 14 - angina of tension of different functional classes. Violation of sexual function also, was noted in 8 patients with unstable and in 14 patients with stable angina. Basically, such violations of sexual function, such as erectile dysfunction (36, 18%) and a decrease in sexual activity (28.46%) occur.

A significant increase in FSH,  $E_2$ , a trend toward an increase in the LH / T ratio was noted. The mean levels of T, LH, PRL did not differ from the corresponding parameters of the control group (Table 1).

**Table 1. The content of serum gonadotropic hormones and androgens in males with IHD**

Patients group	LH, IU/l	FSH, IU/l	PRL, mIU/l	T, nmol/l	E <sub>2</sub> nmol/l	LHT, coefficient
Control (n=18)	6.34±0.93	4.28±0.61	224±31.31	14.53±1.41	220±50	0.83±0.26
I (n=44)	8.3±2.51	8.7±2.67	212.5±51.40	6.67±1.73	240±50	2.04±57
P <sub>1</sub>	>0.5	>0.1	>0.5	<0.01	>0.5	<0.05
Control (n=16)	6.61±1.45	4.41±0.70	168.33±22.53	14.77±0.69	190±40	0.73±0.12
II (n=76)	6.88±0.84	6.92±1.15	166.09±29.51	12.11±2.59	290±40	0.73±0.14
P <sub>2</sub>	>0.5	<0.05	>0.5	>0.1	<0.05	>0.1
P <sub>3</sub>	>0.5	>0.5	>0.5	<0.05	>0.5	<0.05

**Table 2. Dynamics of LH, T, E<sub>2</sub> indices in serum of males with IHD, before and after functional test of testicles with CH**

Patients group	LH, IU/l	T, nmol/l	E <sub>2</sub> pmol/l
I prior to test with CH (n=20)	8,3±2,51	6,67±1,73	240±50
after test with CH (n=12)	5,42±1,26	20,44±4,98	310±80
P <sub>1-2</sub>	> 0,5	<0,01	>0,1
II prior to test with CH (n=34)	6,88±0,84	12,11±2,59	290±40
after test with CH (n=28)	18,0±4,57	18,40±3,11	470±50
P <sub>1-2</sub>	< 0,05	>0,1	<0,002

Changes of the ejaculate and PTH were not found in the first group of patients. FPT with CH – the level of T increased more than 3 times (Table 2)

There is no reliable elevation of T in the blood with FPT in males, patient with IHD in the second age group (Table 2).

Oligozoospermia of Ist. in 12 patients with post infarction cardiosclerosis with relatively high secretion of FSH speaks for the primary lesion of the gonads.

6 patients of II group had a borderline type of PTH, and 4 had obvious mild diabetes mellitus.

Comparing the hormonal parameters of males with IHD in two age groups shows that in males of the I age group the level of T were a lower and a higher LH/T coefficient. With respect to other hormonal indices studied, there were no significant differences between the groups of IHD patients of different ages.

#### 4. CONCLUSION

The obtained data indicate a decrease in testosterone production functions of testicles in patients with IHD, especially expressed at a young age. The hypothalamic-pituitary-adrenal axis is the body's system for regulating the stress response and various organ functions. It consists of the paraventricular nucleus of the

hypothalamus, the pituitary gland and the adrenal cortex [7]. An increase in the LH/T ratio and a low T, as well as an insufficient increase of T in response to stimulation with CH in some patients with post infarction cardiosclerosis testified against the primary lesion of gonads in patients with IHD [8,9]. However, "disinhibition" of increase FSH, LH, gonadotropic pituitary function, even in a young group of patients was insignificant and statistically unreliable.

Based on the obtained data, it is advisable to include testosterone preparations in the complex treatment of patients with IHD, especially at a young age.

#### CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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