

## COMPARISON OF TESTOSTERONE LEVEL IN PATIENTS WITH MYOCARDIAL INFARCTION WITH CONTROL GROUP

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### Contribution

VA conceived the idea and designed the study. MQ did data collection while manuscript writing was done by KI. SNH did the final review. All authors contributed equally to the submitted manuscript.

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### **ABSTRACT**

**Objective:** To compare testosterone levels of patients with myocardial infarction with control group.

**Methods:** In this case control study, the testosterone levels of male patients with myocardial infarction (cases) and men with coronary artery stenosis less than 40% (control group measured by angiography) were compared with each other. This study was done at cardiovascular unit or CCU of Mehr and Aria hospital of Mashhad, Iran from 1st January to 31st December 2015. Serum levels of testosterone of patients with myocardial infarction and control group were recorded and compared with the normal level of testosterone. SPSSv.18 and Statistics V.10 were used, the meaningful level of test was considered less than 5%.

**Results:** This study consisted of 60 participants with 30 in each group. We examined serum samples for testosterone level, the mean serum level in controls and patient groups were 6.7ngr and 2.8ngr/lit respectively. Patient group level was higher than the control group and between the two study groups, there was significant statistical difference ( $p=0.0001$ ). In addition, significant differences in the level of testosterone were observed in both groups according to age stratification. The results showed that 70% of the patients had lower levels of testosterone, but in the control group all were normal.

**Conclusion:** Due to lower testosterone levels in patients with myocardial infarction compared with healthy subjects, it seems that reduced testosterone levels, may be considered as an independent risk factor.

**Key Words:** Myocardial ischemia, Myocardial infarction, Testosterone

## INTRODUCTION

Today, the world of medicine is meeting the growth of chronic diseases; coronary artery diseases in which in the final stages can lead to myocardial infarction, is considered as one of the chronic diseases.<sup>1</sup> Cardiovascular diseases and specifically ischemic heart diseases has been changed to be the recent world's health - related problems in the latest years of the 20th century and the early years of the 21st century, and this global rise is the consequence of unprecedented change in the causes of mortality which is due to industrialization, urbanization and change in the lifestyle.<sup>2</sup> CVD, especially atherosclerosis, have been estimated as the leading diseases around the world by the year 2020. Although, mortality caused by these diseases is decreasing in developed countries due to primary and secondary prevention in the last few decades, the disease is still an important cause of morbidity and the fifth cause of paralysis and disability in most societies. According to official statistics, coronary artery diseases is the main cause of mortality in Iran, and mortality rate due to this phenomenon in Iran and other developing countries is increasing as it will reach to 44.8% by the year 2030.<sup>4,6,7</sup>

Clearly, ischemic heart disease occurs when there is imbalance between supply and demand in myocardium and it shows itself with chest pain.<sup>2,8</sup> In many vascular disorders including atherosclerosis, the role of endothelial cells in intima to be a selective barrier between tissues and blood components is disturbed.<sup>9</sup> Systematic studies on atherosclerosis' risk factors began from the middle of present century.<sup>9</sup> Hypertension, diabetes, smoking, obesity and lipid disorders are of main controllable risk factors of this disease and increase while age and male sex are of uncontrollable risk factors.<sup>4,9,11</sup> Studies, in the last few decades, have shown that the risk of coronary artery disease in males is higher compared to women before menopause.<sup>3,4</sup> Hormones are one of the important factors affecting atherosclerosis and insulin, thyroid hormones, glucocorticoid, and sex hormones disorders with a change in the lipoproteins are involved in this process.<sup>11-13</sup> Some studies express that serum level of testosterone in males is one of the risk factors affecting the increase of CVD incidence.<sup>14</sup>

Testosterone is the dominant androgen in males which 95% of it is produced by Leydig cells in testes, under the control of hypophyseal hormones FSH and LH. The serum level of testosterone reduces with increase in age.<sup>15-18</sup> Generally, testosterone hormone not only affects the reproductive system but also it affects many other organs activities such as cardiovascular system.<sup>19</sup> According to epidemiologic studies, serum levels of this hormone in males has a reverse relationship with the abdominal obesity (waist-hip ratio) and a direct relationship with the amount of HDL.<sup>16</sup> A change in the lipid profile, insulin sensitivity homeostatic mechanisms, sympathetic system regulation, renin-angiotensin-aldosterone system, and direct activities including the moderating effect on the pre-inflammatory enzymes, the production of bio-oxidative reactions, nitric oxide, and regulatory systems for vessel contraction are all among the possible mechanisms of testosterone on cardiovascular system.<sup>14,19,20</sup> According to a study conducted by the Stanworth, men with slightly higher level of testosterone than average, are less exposed to high blood pressure, MI, and obesity.<sup>21</sup> In

addition, the increase of testosterone decreases total cholesterol, LDL and triglycerides levels.<sup>9,21</sup> Many other cross – sectional studies such as study by Elisabeth Wehr and her colleagues, showed that patients with coronary artery diseases have lower levels of testosterone hormone.<sup>22-24</sup> In addition, in many recent studies, as well as the recent study conducted by the Arthi Thirumalai and his colleagues , less ischemic incidence, MI, and mortality have been observed in men with higher levels of testosterone due to the beneficial of TRT<sup>23,25-30</sup>; But there are other studies which have pointed to the susceptible high plasma level and receiving high level of testosterone affecting the risk of cardiovascular diseases.<sup>21,31</sup> Among the few studies on the effect of testosterone on cardiovascular system conducted in Iran, the study conducted by Dr. Kazerani and his colleagues can be pointed out; in which the relationship between androgenic alopecia due to the increase of testosterone level in blood and the incidence of coronary artery diseases has been defined.<sup>32</sup> Also, according to a study done by Dr. Nasir and his colleagues, the level of plasma testosterone in women had no meaningful relationship with the incidence of coronary artery diseases.<sup>33</sup>

Therefore, according to these inconsistent results and the importance of cardiovascular diseases, especially atherosclerosis and myocardial infarction as the first cause of death in most societies, this study tries, for the first time in Iran, to compare the level of testosterone hormone in men with myocardial infarction and healthy men.<sup>7,34</sup>

## METHODOLOGY

In this case control study approved by the ethics committee of Shahinfar Medical College located in the city of Mashhad, patients were investigated from 1st January to 31st December 2015. The patient group included men aged 30-70 years old who were hospitalized in cardiovascular unit or CCU of Mehr and Aria hospital of Mashhad because of heart failure or myocardial infarction. They were selected based on clinical examinations including heart and lung auscultation, examining pulses, blood pressure, and heart and respiratory rates by cardiology experts, confirmed by laboratory criteria of myocardial infarction (exclusive proteins CKMB, cTnT and cTnI) and symptoms of ischemia in ECG including the decline of ST more than 0.1 mV lower than the baseline, the left - bundle block, ventricular Paced or pathogenic Q wave.<sup>4</sup> Control group included men aged 30-70 years old who, after the angiography of coronary arteries, showed less than 40 percent of coronary stenosis; they were screened based on age, risk factors affecting the cardiovascular diseases including high blood pressure, diabetes, smoking, and positive family history of myocardial infarction.

In this study, those who used hormonal medicines, or those with systemic diseases such as diabetes, hyperthyroidism, or chronic diseases which affect the serum levels of testosterone, were excluded.

From both groups blood samples were mostly taken in the morning. After eliminating the hemolyzed or lipemic blood samples, serum was separated from blood samples and were kept in dry ice and sent to Zakaria research center and kept at -18°C; serum levels of testosterone hormone were measured by ELISA method.

After that, the serum levels of testosterone of patients with myocardial infarction and serum levels of testosterone of control group were recorded and compared with the normal level of testosterone (300 to 1000 ngr/lit). The related checklist was completed by the person responsible for gathering samples. In this process, patient's names were confidential.

Finally, data of both groups were compared and then statistical analysis was done. At the first stage, the normality of data was assessed using first test sample of Kolmogorov-Smirnov with Lilliefors adjustment. Considering the approval of data normality, appropriate parametric methods such as Student's test and logistics regression were used in the analysis of data. For the analysis of data with the scale, Chi-Square was used. Incases where more than 20% of expected frequencies were less than 5, (Cochrane) Fisher's Exact Test was used. SPSS v.18 and Statistics V.10 were used in this study, the meaningful level of test was considered less than 5%.

## RESULTS

In this study, 30 men with myocardial infarction and 30 healthy men were investigated. The average age range of men with

myocardial infarction was lower than in control group. There was no statistically significant difference between two groups ( $p = 0.881$ ). Among patients with myocardial infarction there were more smokers than control group but there was not statistically significant difference between two groups ( $p = 0.602$ ). More patients with myocardial infarction suffered from hypertension than people in control group, though there was no statistically significant difference between two groups ( $p=0.432$ ). In control there were more people who had diabetes mellitus with no statistically significant difference between two groups was observed ( $p = 0.317$ ). In control group there were more people with family history of myocardial infarction, again no statistically significant difference between two groups was observed ( $p=0.706$ ).The summary of results have been presented in table 1.

Serum levels of testosterone in patients group were significantly lower than in control group (Table 2) ( $p=0.0001$ ). Also, these results showed that in patients group, 21 (70%) patients had testosterone levels below normal level while in control group all the men had normal level of testosterone.

**Table 1: Demographic Variables of study population (n=60)**

Variable	Control group (n=30)	Patients group (n=30)
Smoking	56.5±8.4	55.9 ± 8.9
Hypertension	(0.40) 12	(46.7) 14
Diabetes mellitus	(46.7) 14	(36.7) 11
Family history of myocardial infarction	(23.3) 7	(13.3) 4
	(16.7) 5	(10.0) 3

**Table 2: Distribution of Serum Levels of Testosterone in study population (n=60)**

	Serum level of testosterone	P Value
Patients	2.8±1.9(0.5-8.0)	
Control	6.7±1.8 (3.2-9.7)	0.0001
Total	4.8±2.7 (0.5-9.7)	

## DISCUSSION

Coronary artery diseases are the most important cardiovascular disorder and a major health problem throughout the world, including the developing countries. In Iran, the first and the most common cause of mortality of all ages and both sexes, is cardiovascular disease, and especially coronary artery disease<sup>1</sup>. On the other hand, the serum level of testosterone in males has a direct relationship with HDL and reverse relationship with central obesity, and thus, it can be suggested that may be the testosterone levels is correlated with ischemic heart diseases.<sup>16</sup> Therefore, in this study, the serum level of testosterone in men with myocardial infarction was compared to healthy men.

The average age range of patient group was 55.9 years and in control group it was 56.5 years according to the results of two groups in terms of the age there was no significant difference between them, after examining the impact of age on the

relationship between testosterone level and myocardial infarction, these two groups showed no significance difference. While, in the study conducted by Chris J Malkin and his colleagues in the 2010, the average age of healthy people considering coronary artery disease was  $55.5 \pm 11.3$  and in patients with coronary artery disease was  $60.7 \pm 9.4$ ; considering  $p= 0.0001$  this difference was statistically significance.<sup>23</sup> J Arnlov and his colleagues came to the conclusion that in middle-aged men compared to young men, higher level of estradiol had protective role.<sup>35</sup> Also, a study done by Bu B Yeap and his colleagues in showed a significant relationship between age and infarction.<sup>36</sup> Perhaps, the reason of this paradox in different studies is due to the influence of demographic variables and risk factors and their importance in the incidence of ischemic heart diseases.

In this study, the average serum level of testosterone in control group was 6.7 ngr/lit and in patient group it was 2.8 ngr/lit which separately, the highest level in control group was 9.7 ngr/lit and in

patients group it was 8 ngr/lit; the lowest level in control group was 3.2 ngr/lit and in patients group it was 0.5 ngr/lit. According to the data analysis there was a significant difference between two groups considering serum level of testosterone ( $p = 0.0001$ ). Also, after the breakdown of age groups to less than 55 years ( $n = 35$ ), a significant difference was observed between two groups considering testosterone levels. Veronique Soisson and his colleagues found that the higher and lower levels than the normal range of plasma testosterone is associated with higher risk of coronary artery disease in elderly men and desirable range of plasma reduces risk of cardiovascular diseases, this suggests the necessity of correcting the shortage of testosterone in patients.<sup>37</sup> A study by Dr. Hu X and his colleagues showed that the serum level of testosterone in patients with myocardial infarction is less than control group which shows that middle aged patients with coronary artery diseases have lower level of testosterone and the serum level of this hormone has a reverse relationship with coronary arteries stenosis.<sup>38</sup> Also, Dr. Wehr E and his colleagues found that the low level of free testosterone, independently, is related with the increase in mortality rate due to heart congestion.<sup>24</sup> Dr. Claes O and his colleagues found that the higher level of testosterone is related with the risk reduction of fatal and nonfatal cardiovascular diseases in middle aged men<sup>14</sup>. While, in the study, by Dr. Molly M Shores and his colleagues there was no relationship between total and free levels of testosterone with infarction, whereas DHT showed nonlinear relationship with infarction ( $p = 0.006$ ) and the lowest risk of stroke was at the level of 50 - 75 ngr/lit.<sup>39</sup> In the multivariate study done by Dr. Bu B Yeap and his colleagues, no relationship between testosterone level and estradiol with MI incidence was found, but testosterone and dihydrotestosterone showed relationship with the reduction of infarction risk.<sup>36</sup> The study by Dr. Gail A and his colleagues showed that estradiol is a strong predictor for carotid involvement in middle aged men and it is a risk factor for atherosclerosis.<sup>27</sup> In Iran, Dr. Kazerani and his colleagues investigated the relationship between ischemic heart diseases and early androgenic alopecia in males. According to the significant relationship between the two mentioned factors it can be concluded that vertex alopecia, through the increase of blood testosterone, causes atherosclerosis exacerbation and coronary artery disease.<sup>32</sup>

According to the results, the lower serum level of testosterone in patients with myocardial infarction compared to people with healthy coronary arteries confirmed by angiography which was done in Iran for the first time, and also, considering the results of other studies in Sweden, Japan, the United States of America, and Norway, it seems that the low serum level of testosterone, like other risk factors affecting the cardiovascular events, should be considered as an independent risk factor affecting other risk factors; this can help the diagnosis and serious and more accurate follow-up males with low level of testosterone in order to prevent ischemic heart diseases as the most common cause of death in Iran.

## CONCLUSION:

Due to lower testosterone levels in patients with myocardial infarction compared with healthy subjects, it seems that reduced testosterone levels, may be considered as an independent risk factor.

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