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Correlation between Free Testosterone and Severity of Coronary Artery Disease in Young Adult Male Patients

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Abstract Historically, High level of serum testosterone was thought to have deleterious effect on cardiovascular system. In the last few years, studies have suggested that low testosterone levels are associated with increase prevalence of risk factors for cardiovascular diseases. This study aimed to determine the relationship between free testosterone level and the angiographic severity of coronary artery disease in young adult male patients. This cross-sectional study was conducted at Department of Laboratory Medicine in collaboration with Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh from March, 2020 to February, 2021. Total 110 subjects from inpatient Department of Cardiology were enrolled, 60 were CAD patients and 50 were Normal Coronaries according to coronary angiography report. Serum level of free testosterone was significantly lower in CAD group than Normal coronaries (4.74±2.10 vs 9.36±3.69 pg/ml, p=0.001). There were significant negative correlation between free testosterone with Gensini score (r= -0.739, p=0.001). Low level of free testosterone was negatively correlated with CAD and its severity in young adult male.

Keywords: *Coronary artery diseases, Gensini score, free testosterone, young adult male*

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1. Introduction

Coronary artery disease (CAD) is a major cause of death and is a global health problem reaching epidemic in both developed as well as in developing countries [1]. CAD is the most common form of heart disease. Men are at higher risk for CAD compared to women. Men have 3 fold increased risk of developing CAD than women and men often develop CAD approximately 10 years earlier than women [2]. In majority of patients, atherosclerosis is the main etiopathogenic process that leads to CAD but there are multiple non-atherosclerotic causes such as congenital coronary artery anomalies, coronary artery spasm, dissection, embolism, arteritis, vasculitis and trauma [3]. CAD is influenced by various risk factors such as high level LDL, low level HDL, cigarette smoking, hypertension, diabetes etc [4]. Testosterone is a steroid hormone synthesized predominantly by the testicular Leydig cells under the control of the gonadotropins, chiefly luteinizing hormone. Testosterone secretion demonstrates both diurnal and circannual variation, peak in the early morning and in the autumn. About 68% of testosterone in blood bound tightly to sex hormone binding globulin, 30% weakly bound to albumin and remaining 2% circulates freely. This free testosterone along with the albumin bound portion that make up the biologically available testosterone to the tissues [2]. The Baltimore Longitudinal Study of Ageing suggests that both total and free testosterone level decline with age [5]. Total testosterone level fall at an average of 1.6% per year while free and bioavailable testosterone levels fall by 2%-3% per year because aging is also associated with increase in sex hormone binding globulin levels [6]. Free testosterone is able to diffuse into the cytoplasm and bind to its specific receptor. It is more useful when the sex hormone binding globulin level is decreased. Free

testosterone is more specific in obese or older patient [7]. It was observed that testosterone modifies cardiovascular risk factors, particularly the lipid profile, blood pressure, body mass index (BMI) and obesity [8,9,10]. Low testosterone level is associated with raised pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6 and reduced anti-inflammatory cytokines like interleukin-10 which are in turn associated with pro-atherosclerotic and inflammatory states. Additionally, it is also associated with raised fibrinogen and hypercoagulable states which promotes atherosclerosis and atherosclerotic plaque instability and acute coronary syndromes [11]. Testosterone deficiency is associated with loss of bone and lean body mass, increased adiposity, low energy, impaired physical and sexual function [12]. Normal physiological level of testosterone is beneficial to the male cardiovascular system (CVS). Testosterone deficiency is associated with an unfavorable metabolic profile including increased adiposity, insulin resistance, diabetes and increased cardiovascular disease events such as myocardial infarction [13]. Serum testosterone has a direct relationship with plasma high-density lipoprotein (HDL) cholesterol and an inverse relationship with low-density lipoprotein (LDL) cholesterol, total cholesterol and triglycerides [14]. Epidemiologic studies have found that low serum testosterone levels are associated with atherosclerosis, CAD and cardiovascular diseases events [15,16]. Some studies show that testosterone supplementation in the elderly and middle-aged males with hypogonadism improves a better cardiovascular state and slowing of the atherosclerosis process [13]. Therefore, it is necessary to identify other risk factors for CAD that may enhance the classical cardiovascular risk factors. Considering the above-mentioned points, this study aimed to investigate whether serum free testosterone level in males with CAD is lower than that with normal coronary.

2. Materials and Methods

This cross-sectional study was conducted at Department of Laboratory Medicine in collaboration with Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh from March 2020 to February 2021. Total 110 subjects from inpatient Department of Cardiology were enrolled, 60 were CAD patients and 50 were normal coronaries according to coronary angiography report. Young adult male (18-40 years) patients presented with acute coronary syndrome admitted into CCU at BSMMU and NICVD were included in this study. The exclusion criteria included history of known case of CAD or myocardial infarction, renal failure, hepatic failure, respiratory failure, testosterone therapy, malignancy, presence of acute illness, use of medications that affect sexual hormones, such as anticonvulsants and antithyroid drugs, valvular and congenital heart disease, cardiomegaly, previous history of angioplasty, major trauma or surgery within 3 months. After selection, all the patients were thoroughly informed about the aims, objectives and procedure of the study and were encouraged for their voluntary participation. Informed written consent was taken from each subject. A detail personal, medical, occupational, educational and smoking history were recorded in a preformed data sheet and thorough physical examinations were done and documented. Physiological measurements were recorded at baseline for all participants. After an overnight fasting venous blood samples were obtained on the day of the coronary angiography in order to measure serum biochemistry. Investigations were done in Department of Laboratory Medicine, BSMMU. Serum free testosterone level was assessed from stored separated serum by enzyme-linked immunosorbent assay (ELISA). Collected blood samples were run in each successive day for serum lipid profile and fasting plasma glucose. The serum lipid profile and fasting plasma glucose were assessed by automated biochemistry analyzer SIEMENS Dimension EXL with LM by the principle of photometric. Presence of CAD was confirmed by conventional angiography and analyzed for presence, extent and severity of CAD. Severity of CAD was expressed by Gensini score. The angiography was performed in the cath-lab under local anesthesia by an expert cardiologist. Statistical analysis were carried out by using the Statistical Package for Social Sciences version 23.0. The mean values were calculated for continuous variables. ANOVA test was used to compare the groups based on vessels score and Spearman's correlation co-efficient test was done to assess the relationship between free testosterone and Gensini Score.

3. Results

Out of total of 110 subjects, 60 (54.54%) with CAD were compared with 50 (45.46%) normal coronary subjects. Baseline and clinical characteristics of CAD group and normal coronaries group are displayed in Table 1. Patients with CAD have higher significant hypertension, diabetes mellitus and dyslipidemia than normal coronaries. In the lipid profile, HDL and triglyceride were significantly difference between CAD and normal coronaries. More importantly, serum free testosterone (pg/ml) was significantly ($p=0.001$) lower in CAD (4.74±2.10) than normal coronaries (9.36±3.69) (Table 1).

Among 60 CAD patients, 10 were single vessel disease, 17 were double vessel disease and 33 were triple vessel disease. The results of the comparison between the Gensini score and free testosterone within CAD group based on the number of affected vessels were summarized in Table 2. There was a significant association between the level of free testosterone and the number of affected vessels within CAD group. Patients with triple vessel disease had lower level of free testosterone compared to those with double and single vessel disease ($p<0.05$). The mean Gensini score was higher in patients with triple vessel disease compared to those with double and single vessel disease. There were significant increasing trend in the number of subjects with low serum free testosterone level based on the vessel score and degree of involvement (Table 2).

Table 1. Baseline and clinical characteristics of study population (N=110)

Variables	CAD (n=60)	Normal Coronaries (n=50)	p value
Age (year)	37.72±2.73	37.48±2.54	0.64
BMI	25.74±2.68	25.66±2.90	0.50
Systolic BP (mmHg)	138.58 ± 25.59	133.60 ± 16.22	0.236
Diastolic BP (mmHg)	86.5 ± 12.63	85.4 ± 12.64	0.650
Pulse (/min)	80.35 ± 9.93	77.83 ± 9.63	0.163
Smoking(%)	45 (75%)	30 (60%)	0.093
Hypertension(%)	48 (80%)	28 (56%)	0.008[s]
Diabetes mellitus(%)	37 (61.67%)	13 (26%)	0.001[s]
Family History of CAD(%)	36 (60%)	26 (52%)	0.527
Dyslipidemia(%)	52(86.66%)	29(58%)	0.001[s]
Total Cholesterol (mg/dl)	185.95±51.35	177.98±42.67	0.375
HDL (mg/dl)	32.25±5.02	35.78±5.84	0.001[s]
LDL (mg/dl)	110.56±43.38	108.36±32.39	0.762
Triglyceride (mg/dl)	212.22±116.8	160.86±96.65	0.013[s]
FBS (mmol/L)	7.29± 1.95	6.71± 2.08	0.131
Serum Free Testosterone (pg/ml)	4.74±2.10	9.36±3.69	0.001[s]

p-value<0.05 was significant, s=significant, Data were presented as mean ±SD for continuous variables. BMI=Body mass index, BP=Blood pressure, CAD=Coronary artery disease, HDL=High density lipoprotein, LDL=Low density lipoprotein, FBS= Fasting blood sugar.

Table 2. Association of Gensini score and free testosterone level with type of vessel disease in CAD (N=60)

Type of Vessel Disease	Single(n=10)	Double(n=17)	Triple(n=33)	p-value
Gensini score (Mean± SD)	20.70±14.14	40.67±25.13	56.06±23.80	0.001[s]
Free testosterone(pg/ml) (Mean± SD)	6.86±3.54	5.16±1.98	3.88±0.65	0.001[s]

p-value<0.05 was significant, ANOVA test was done, s=Significant, Data were expressed as mean±SD.

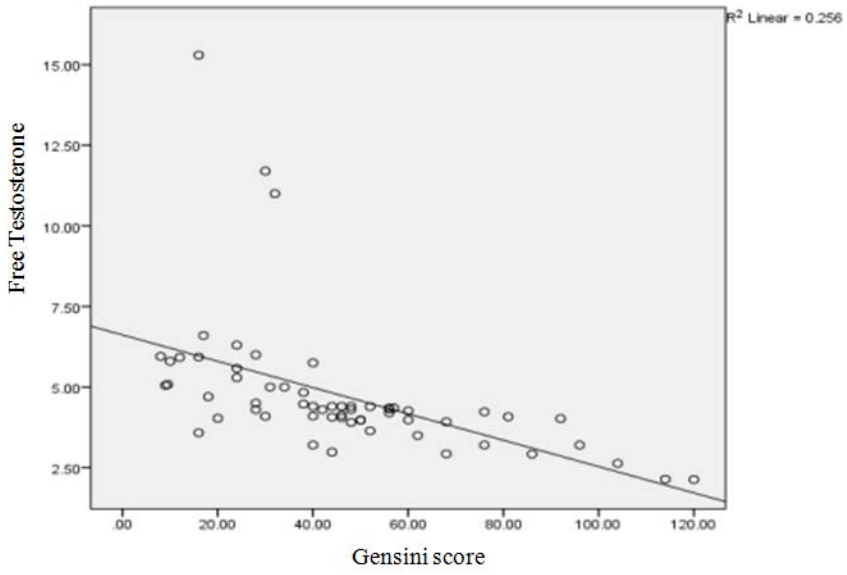

Figure 1. Scatter diagram showing a significant negative correlation between serum free testosterone levels and Gensini score in CAD (r= -0.739, p=0.001)

In order to remove the effect of potential cofounder like hypertension, diabetes mellitus and dyslipidemia, a multivariate logistic regression analysis was done and it showed a significant association between CAD and free testosterone (OR=6.032, 95% CI: 1.876-26.073, p-value=0.001) (Table 3).

Table 3. Independent predictors for severity of coronary artery disease by multivariate logistic regression analysis.

Variables of interest	Regression co-efficient	Odds Ratio, OR	95% CI of OR	p-value
Hypertension	0.817	2.264	0.842-6.087	0.842
Diabetes Mellitus	0.642	1.899	0.720-5.014	0.195
Dyslipidemia	0.320	0.674	0.194-2.718	0.634
Low serum free testosterone level	1.98	6.032	1.876-26.073	0.001[s]

p-value<0.05 was significant, s=Significant.

4. Discussion

In the present study, we found that free testosterone was lower and negatively correlated to the severity of coronary artery disease. This result was consistent with previous studies [17,18]. These results suggesting that endogenous testosterone may have an inhibitory effect on progression of atherosclerotic CAD. Previous studies demonstrated that serum low testosterone level is associated with markers of atherosclerosis such as impaired endothelial vasomotor function, increased carotid intima-media thickness and aortic calcification [19,20,21]. Although the exact mechanism of the beneficial effects that testosterone exerts on atherosclerosis has not yet been understood, it is proposed that it may cause coronary vasodilatation directly by metabolic pathways or after peripheral conversion of testosterone to estrogen in the adipose tissue. Estrogen may exhibit vascular effects and slow down the progression of atherogenesis in men [22,23,24]. Testosterone levels are negatively correlated with insulin, fibrinogen and plasminogen activator inhibitor-1 in men with CAD [17]. The relatively hypercoagulable state induced by low free testosterone may have contributory effect to atherosclerosis development. Additionally, patients with low testosterone levels have been found to have impaired endothelial function which may contribute to the increased cardiovascular risk in them [21,25]. Some studies reported that low-dose testosterone therapy in men with CAD reverses exercise-induced myocardial ischemia and acute intravenous testosterone administration has anti-ischemic effects [22,24,26]. Akishita et al. suggested that endogenous testosterone may have a protective effect against cardiovascular disease in men; specifically, testosterone could benefit endothelial function, elicit vasodilation and increase blood flow in men [24] and in animals [27]. Some studies suggested that an increased frequency of thromboembolic events has also been reported in androgen deprived men [28,29]. These findings provide evidence for the role of endogenous testosterone in the severity of CAD. The pathophysiology of cardiovascular risk of low testosterone level may be related to increased fat mass [30]. Serum testosterone levels have a direct relationship with HDL and an inverse relationship with LDL, total cholesterol and triglyceride [14]. The mechanisms underlying the effects of testosterone on lipid profile is still not fully clear. However, there is evidence from studies of animal, cells and clinical which suggested that testosterone controls the expression of important regulatory proteins involved in lipid and cholesterol metabolism [31]. The mechanism may be that testosterone directly affects HDL by increasing the production of apolipoprotein A-I [32]. Apolipoprotein A-I is the major component of newly synthesized HDL [33]. The inverse relationship between testosterone and TG also suggests that some influence of testosterone on HDL may be mediated through the TG levels [34]. Taking these results into consideration, it may be said that low serum free testosterone level has significant correlation not only with CAD but also with its severity. It may be used as a simple biochemical diagnostic tool for clinical use to assess CAD in young patient and it can be done in small laboratory facilities in our country.

5. Conclusion

Serum free testosterone was significantly lower in the young male with CAD than normal coronary subjects and free testosterone level was negatively correlated with angiographic severity of coronary artery disease. In this regard, serum free testosterone may be used as an important biochemical tool to assess the severity of CAD. Therefore, it will be greatly beneficial for clinicians to assess severity of CAD to start treatment earlier. Based on this result, low level of free testosterone may be used as a predictor for coronary artery disease in young adult male.

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Conflicts of Interest

No conflict of interest relevant to this article was reported.

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