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Association between Serum Testosterone Levels and Premature Coronary Artery Disease among Young Adult Males

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Abstract

Introduction: Prevalence of coronary artery (CAD) disease is increasing day by day among the young adult male population in Bangladesh. The most notable features of CAD in this population are the extreme prematurity and severity and 5-10-fold higher rates of myocardial infarction and death before the age of 40 years. There are a lot of modifiable and non-modifiable risk factors for developing CAD in young adults. Male sex and male sex hormones are also important risk factors, but studies regarding the association with testosterone levels are done yet in our country. The aim of the study was to observe the possible association between serum testosterone levels and premature coronary artery disease.

Methods: This cross-sectional study was conducted at the Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh. The study duration was 1 year, from October 2018 to September 2019. A total of 100 cases were selected among the patients with Chronic Stable Angina (CSA) and Unstable Angina (UA) who underwent coronary angiography at the study hospital following the inclusion and exclusion criteria. The purposive sampling method was used for the selection of the participants, and the total participants were divided into two equal groups of 50 patients each, where Group 1 included 50 patients with low serum testosterone levels, and group 2 included 50 patients with normal serum testosterone levels.

Result: A total number of 100 patients were studied, divided into two equal groups of 50 cases in group I and 50 control in group II. The mean age of the studied patients was 39.9±5.2 years ranging from 26 to 45 years. The mean age of the group I patients were 39.9±5.9 years ranging from26 to 45 years and the mean age of the group II patients was 40.0±4.5 years ranging from 30 to 45 years. Mean serum testosterone level had decreased as the number of vessels involved increased in normal, single, double and triple vessel disease being 3.91, 2.65, 2.08, and 2.02 respectively and the difference was statistically significant ($p<0.001$).

Conclusion: This study found a link between testosterone levels and premature coronary artery disease in young adult males, and testosterone levels are connected with angiographic severity of premature coronary artery disease. Our findings show that decreased testosterone levels may be a new cardiovascular risk factor for developing early coronary artery disease.

Keywords: Coronary; Heart; Serum; Testosterone; Myocardial Infraction.

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Introduction

Coronary artery disease (CAD) is a worldwide public health crisis and the main cause of death and morbidity. Cardiovascular disease accounts for 30% of all fatalities worldwide, with CAD accounting for more than half. Globally, of those dying from cardiovascular diseases, 80 percent are in developing countries [1]. Ischemic Heart Disease (IHD) is a major and increasing health care issue in Bangladesh [2]. The exact prevalence of CAD in Bangladesh is not known. More recent data indicate CAD prevalence between 1.85% to 3.4% of the total population [3]. IHD has been classified as chronic IHD, acute coronary syndromes, and sudden death. IHD may present clinically in many ways, extending from an asymptomatic finding to unexpected cardiac collapse. Acute coronary syndrome (ACS) is a catch-all phrase for a common end consequence, acute myocardial ischemia. It encompasses acute MI and unstable angina [1]. Prevalence of this type of CAD is increasing in young adults and is called as premature CAD. Premature CAD is defined as the presence of coronary artery disease at ≤45 years in men and ≤55 years in women. The prevalence and magnitude of the classical cardiovascular risk factors seem to be more prominent in patients with premature CAD and their first-degree relatives. Other common risk factors include the male gender, increasing age, familial hypercholesterolemia, premature atherosclerosis, smoking, family history of early onset of CAD, recreational drug abuse, male and female sex hormones, etc [4]. Testosterone is one such sex hormone that might influence the prevalence of cardiac diseases like CAD. Testosterone is a steroid hormone that is primarily generated by the testicular Leydig cells under the guidance of gonadotrophins, primarily luteinizing hormone. Once generated, it circulates attached to serum proteins, with around 68 percent firmly bound to sex hormone-binding globulin and 30 percent linked more loosely to albumin, leaving just about 2% free to circulate, making up the physiologically accessible (bioavailable) testosterone [5]. Current data shows that testosterone level declines with advancing age in men and is associated with age-related diseases. During male aging, serum testosterone level gradually declines, and the risk of cardiovascular diseases especially CAD increases. Though the male aging process starts after puberty, it can be presumed that the decline of testosterone levels starts at a younger age than is generally expected. Harman et al. investigated the nature and potential etiological factors involve in the change of sex hormone levels with aging [6]. Men have a naturally more pro-atherogenic lipid profile than women, which has previously been linked to greater circulating testosterone levels. Poor lipid profiles have been associated with low testosterone levels rather than normal or high testosterone levels. Testosterone levels have been found to be favorably correlated with cardioprotective high-density lipoprotein (HDL) cholesterol and adversely correlated with atherogenic low-density lipoprotein (LDL) cholesterol and triglycerides. Low testosterone has been linked to a decrease in heart-healthy HDL cholesterol, according to several pieces of research. Low testosterone is also linked to increased fibrinogen levels and hypercoagulable states, both of which cause atherosclerosis, atherosclerotic plaque instability, and acute coronary syndromes [7].

Objective:

General Objective

- To observe the association between serum testosterone levels and premature coronary artery disease

Methods

This cross-sectional study was conducted at the Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh. The study duration was 1 year, from October 2018 to September 2019. A total of 100 cases were selected among the patients with Chronic Stable Angina (CSA) and Unstable Angina (UA) who underwent coronary angiography at the study hospital following the inclusion and exclusion criteria. A purposive sampling method was used for the selection of the participants, and the total participants were divided into two equal groups of 50 patients each, where Group 1 included 50 patients with low serum testosterone levels, and group 2 included 50 patients with normal serum testosterone levels. Informed written consent was taken from each patient before enrollment. Ethical approval was also obtained from the ethical review committee of the study hospital. Meticulous history was taken and detailed clinical examinations were performed and recorded in a predesigned structured format.

Inclusion Criteria

- Male Patients
- Age between 18 to 45 years
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Previously known cases of CAD or myocardial infarction
- Renal or hepatic impairment
- Known case of malignancy
- Use of testosterone therapy or medication that affects testosterone level.
- Associated with valvular and congenital heart disease.

Results

Group I= Patients with low serum testosterone level

Group II= Patients with normal serum testosterone level

ns= Not significant ($p>0.05$)

p-value reached from unpaired Student's t-test.

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Table 1: Age distribution of the study subjects (N=100)

Age in years	Group I (n= 50)		Group II (n=50)		Total (N=100)	p-value
	Number	%	Number	%	Number	
26 – 35	12	24.0	8	16.0	20	N.A
36 – 45	38	76.0	42	84.0	80	
Mean ± SD (Range)	39.9±5.9		40.0±4.5		39.9±5.2	0.91^{ns}
	(26-45)		(30-45)		(26-45)	

Group I= Patients with low serum testosterone level
Group II= Patients with normal serum testosterone level
ns= Not significant (p>0.05)
p-value reached from unpaired Student's t-test.

Table 2: BMI status of the study subjects (N=100)

Body Mass Index Kg/m2	Group I (n= 50)		Group II (n=50)		p-value
	Number	%	Number	%	
18.5 – 22.9 (Normal weight)	10	20.0	16	32.0	N.A
23 – 24.9 (Overweight)	20	40.0	28	56.0	
>25 (Obese)	20	40.0	6	12.0	
Mean ± SD	**24.9±2.4**		**23.4±1.9**		**0.001^{s}**

Group I= Patients with low serum testosterone level
Group II= Patients with normal serum testosterone level
p-value reached from unpaired t test s = Significant (p<0.05)

Table 3: Biochemical parameter of the study subjects (N=100)

Biochemical parameters	Group I (n= 50)	Group II (n=50)	P value
	Mean ± SD	Mean ± SD	
RBS (mmol/L)	9.4±4.3	7.0±2.7	**0.001s**
Serum testosterone level (ng/ml)	2.1±0.2	3.7±0.8	**<0.001s**
Total Cholesterol mg/dl	210.5±31.2	201.7±28.9	0.45^{ns}
Triglyceride mg/dl	156.9±29.5	154.9±28.6	0.51^{ns}
LDL cholesterol mg/dl	118.8±20.6	117.9±19.9	0.61^{ns}
HDL cholesterol mg/dl	38.6±8.1	42.4±11.3	0.26^{ns}

Group I= Patients with low serum testosterone level
Group II= Patients with normal serum testosterone level
p-value reached from unpaired t test
s= Significant (p<0.05); ns = Not significant (p>0.05)

Table 4: Risk factors of premature CVD among the study subjects

Risk Factors	Group I (n= 50)		Group II (n=50)		Total (N=100)		p-value
	Number	%	Number	%	Number	%	
Smoking	40	80.0	27	54.0	67	67.0	**0.006^{s}**
Hypertension	26	52.0	22	44.0	48	48.0	0.42^{ns}
Diabetes mellitus	28	56.0	16	32.0	44	44.0	**0.01^{s}**
Family H/O of CAD	17	34.0	12	24.0	29	29.0	0.27^{ns}
Obesity	20	40.0	6	12.0	26	26.0	**0.006^{s}**

Group I= Patients with low serum testosterone level
Group II= Patients with normal serum testosterone level
p-value reached from Chi-Square test
ns = Not significant (p>0.05), s= Significant (p<0.05)

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The above table shows that a total of 100 patients were studied. The mean age of the total studied patients was 39.9±5.2 years, ranging from 26 to 45 years. The mean age of the group I patients were 39.9±5.9 years ranging from 26 to 45 years and the mean age of the group II patients was 40.0±4.5 years ranging from 30 to 45 years. The mean age of group I and group II was almost identical with statistically no significant difference (p=0.91). It was found that among the group I patients, the highest percentage was in the range of 36-45 years (76%) followed by 26-35 years 24%. The same sequence was observed in group II subjects, where 84% were in the age group of 36-45 years and 16% of patients were in the age group of 26-35 years.

The above table exhibits the body mass index of the participants. The mean age of group I participants was 24.9±2.4 kg/m2 and that of group II participants was 23.4±1.9 kg/m2. Mean BMI was higher in group I than in group II. A significant difference was found between the groups in terms of mean BMI (p=0.001).

The above table explains the biochemical status of the study subjects. The mean random blood sugar was 9.4±4.3 mmol/L in group I, and 7.0±2.1 mmol/L in group II. The difference was statistically significant (p=0.001). The mean serum testosterone level was 3.7±0.8 ng/ml in group II and 2.1±0.2 ng/ml in group I patients with a significant difference (p<0.001). The remaining biochemical characteristics were found almost similar in both groups of patients with no significant difference (p>0.05).

Among the studied patients, the prevalence of smokers was higher in group I than in group II (80% vs. 54%) with a significant association (p=0.006). Hypertension was higher in group I than in group II (52% vs. 44%) with an insignificant association (p=0.42). Diabetes mellitus also had a higher prevalence in group I than in group II (56% vs. 32%) with a significant association (p=0.01). Family history of CAD had a higher prevalence in group I than in group II with insignificant association (p=027). Incidence of obesity was significantly higher in group I than in group II (40% vs. 12.0%, p=0.006).

The table depicts that the mean serum testosterone level had lowered as the number of vessels involved increased. It was observed that in normal, single, double, and triple vessel disease, the mean serum testosterone level was 3.91, 2.65, 2.08, and 2.02 respectively, and the difference was statistically significant (p<0.001) by ANOVA test. The table indicates that the severity of CAD increased with the decreased level of serum testosterone level.

Multivariate logistic regression analysis was done to assess the severity of CAD by independent risk factors. The analysis included traditional risk factors such as smoking, diabetes mellitus, obesity, increased RBS, and low levels of serum testosterone. The result showed that a low level of serum testosterone was the only independent variable that had high significance with severe coronary artery diseases, with OR=5.97, 95% CI-1.998-18.784, p<0.001.

Table 5: Comparison of mean serum testosterone level according to number of vessels involved (N=100)

No. of vessel involved	Serum testosterone level ng/ml		P-value
	Mean	SD	
Normal (n=40)	3.91	0.65	**<0.001[s]**
Single (n=28)	2.65	0.92	
Double (n=18)	2.08	0.23	
Triple (n=14)	2.02	0.23	

s=Significant
P-value reached from the ANOVA test.

Table 6: Independent predictors for severe coronary artery disease by multivariate logistic regression analysis

Variables of interest	Regression coefficient (β)	Odds Ratio (OR)	95% CI of OR	p-value
Smoking	1.268	3.55	0.989 – 11.991	0.06[ns]
Diabetes mellitus	-0.974	0.377	0.084 – 1.697	0.20[ns]
Obesity	-0.22	0.802	0.203 – 3.170	0.75[ns]
Increased RBS	0.113	1.12	0.896 – 1.399	0.32[ns]
Low level of serum testosterone (<2.5 ng/ml)	**3.032**	**5.97**	**1.998 – 18.784**	**<0.001s**

*Not significant (p>0.05)
** Significant (p<0.05)

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Discussion

The mean age of the studied subjects was 39.9±5.2 years ranging from 26 to 45 years. The mean age of the group I patients were 39.9±5.9 years ranging from 26 to 45 years and the mean age of the group II patients was 40.0±4.5 years ranging from 30 to 45 years. In a study in Sri Lanka, the mean age of the premature CAD group was 32 to 45 years and for the control group, it was 30 to 45 years, while the mean ages of the two groups were 41 ± 3 vs. 37 ± 4 years, which was more or less similar to this study [8]. Another study by Alkamel et al. showed a slightly higher mean age among the CAD participants, but the mean age of the control group was almost identical to our study [9]. The mean body mass index (BMI) of group I was 24.9±2.4 and that of group II was 23.4±1.9. Mean BMI was higher in group I than in group II and a statistically significant difference was found between the groups in terms of BMI (p=0.001). According to these findings, high BMI is associated with increased severity of premature CAD, which was supported by the findings of Marcial et al [10]. The biochemical parameters of the study subjects were compared between the two groups. The mean values of clinical parameters like pulse, systolic blood pressure, and diastolic blood pressure were similar between the two groups and there was no statistically significant value between them. However, the mean random blood sugar was (9.4±4.3) mmol/L in group I, and (7.0±2.1) mmol/L in group II. The difference was statistically significant (p=0.001). In a 2016 Indian study, the authors found fasting and postprandial blood sugar were higher in low-level testosterone patients in relation to the control group, and it was statistically significant [11]. A statistically significant difference was also found between the serum testosterone levels of the two groups, with the group I having serum testosterone levels of 2.1 ± 0.2 ng/ml and group II having 3.7 ± 0.8 ng/ml. The rate of the smoker was higher in group I than in group II (80% vs. 54%) and a statistically significant association (p=0.006) was present. Smoking is one of the most common risk factors for developing CAD among the younger population. According to Framingham research, smokers have a higher risk of myocardial infarction (MI) or sudden death, and this risk is linked to the number of cigarettes smoked each day [12]. Other epidemiological investigations corroborated these findings. For smokers under the age of 50 years, the risk of developing CHD is 10 times greater than for nonsmokers of the same age [13]. Prevalence of Hypertension was higher in group I than in group II (52% vs. 44%), but it was statistically insignificant (p=0.42). Hypertension is a major modifiable risk factor for premature CAD. Though it was not statistically significant in this study, it was clear that subjects having low testosterone levels were more hypertensive than subjects with normal testosterone levels. Diabetes mellitus also had a higher prevalence in group I than in group II (56% vs. 32%), with a statistically significant difference. It denotes DM is an important risk factor for developing premature CAD in young adult males in this study. Indirectly it is said that subjects having low testosterone levels are more prone to develop DM and ultimately early initiation of CAD. In the present study, we also found a significant correlation between lower serum testosterone levels and the number of coronary vessel involvement. It was observed that the mean serum testosterone level decreased as the number of vessels involved increased. Multiple risk factors like diabetes mellitus, and smoking. Obesity, RBS, and low serum testosterone level were found to be a significant association with the development of premature CAD and were present statistically by risk analysis. Then Multivariate logistic regression analysis was done to assess the severity of CAD by independent risk factors including traditional risk factors such as smoking, diabetes mellitus, obesity, increased RBS, and low level of serum testosterone. After removing the effect of Diabetes mellitus, obesity smoking, and RBS, the result showed that a highly significant association was present between low levels of serum testosterone and CAD, with OR=5.97, 95% CI-1.998-18.784, and p<0.001. The findings of this study were supported by several other studies [9, 11].

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. The sampling method was not random but purposive, so there is a risk of selection bias.

Conclusion

This study found a link between testosterone levels and premature coronary artery disease in young adult males, and testosterone levels are connected with angiographic severity of premature coronary artery disease. Our findings show that decreased testosterone levels may be a new cardiovascular risk factor for developing early coronary artery disease.

Recommendation

Study recommend multi-centre study with large sample size to draw a more realistic findinhgs for the selected issue.

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Conflict of interest: None declared.

Ethical approval: The study was approved by the Institutional Ethics Committee.

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