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Relationship Between Serum Total Testosterone and Coronary Artery Disease in Men

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ABSTRACT

Background: Male sex has always been considered as an independent risk factor for cardiovascular disease. But recent studies have shown controversial results. This study aimed to investigate the relation of serum testosterone withrisk factors of coronary artery diseasesand with degree of severity of coronary artery stenosisin men with coronary artery diseases.

Methods: After applying inclusion and exclusion criteria 102 men (aged 60.42 += 11.11), were included. Fasting blood sample were obtained and blood sugar, total testosterone and lipid profile were measured. Severity of coronary stenosis was estimated by Gensini score. The relationships were assessed using chi-square test, one way analysis of variance and Pearson's Correlation.

Results: Of the total 102 patients, majority of them 42 (41.2%) had triple vessel disease. Testosterone (nmol/L) was found to be 12.01 ± 6.1. Cardiovascular diseaserisk factors like age, body mass index etc. were found to be negatively correlated with testosterone but not statistically significant. Likewise, Gensini score also correlated negatively with testosteronebut not up to the threshold of statistical significance (r=-0.069, p-value = 0.496). Similar results were obtained when number of vessels involved and testosterone were compared. However, the number of diabetic patients gradually decreased with the increasing value of testosterone in the three tertile group (p-value = 0.040).

Conclusions: This study could not find significant association between testosterone and coronary artery diseases, however low testosterone was associated with diabetes mellitus.

Keywords: Coronary artery diseases; diabetes mellitus; gensini score; testosterone.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally. According to world health organization (WHO), the death rate has reached 152.6 per 100,000 population, ranking Nepal at position 47 in the world.[1]

Recent studies have reported that low testosterone is an independent risk factor for CVD.[2, 3] The exact mechanism isnot known but testosterone is thought to negatively affect the components of the metabolic syndrome and cause vasodilatation of coronary arteries, both in vitro and in vivo.[4, 5] Besides, factors like hypercholesterolemia, diabetes, etc. had been assumed to be major determinants of CAD but studies have failed to show their relationwith degree of severity of CAD.[6]

In Nepalese population the association of testosterone with CAD is unknown. Therefore, this study aimed to find the relation between testosterone and degree of severity of CAD and its risk factors such as lipid levels and diabetes.

METHODS

This cross sectional, observational study was conducted in Department of Biochemistry, Maharajgunj Medical Campus; Manmohan Cardiothoracic Vascular and Transplant Center (MCVTC); Institute of Medicine (IOM), Tribhuvan University Teaching Hospital, Kathmandu,

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Nepal and its clinical laboratory.All male patients who presented to the MCVTC between March and August 2015, with CAD (angiographically proven), who provide written consent for the study were included. Patient on any medication affecting sex hormone level like anticonvulsant and antithyroid drugs, with carcinoma of prostrate or prostatectomy, major organ failure (respiratory/renal/liver), history of recent surgery or major trauma (within 3 months) and previous angioplasty were excluded. In this study,non-probability (convenience)sampling was done and a total of 107 patients were included.Out of these, 5 had recently undergone angioplasty so they were excluded from the study.

The ethical clearance was obtained from the Institutional review committee of IOM, Teaching Hospital, Kathmandu, Nepal. In this study, angiographically proven CAD diseased patient admitted in ward, intensive care unit and cardiac care unit were explained about the research and those who provided written consent to participate in all parts of the study (including an interviewer-administered questionnaire, clinical examination and a blood sample) were included. Blood samples were collected for various tests which were done without financial implication to the patient.Throughout this study, there was no risk for human participants and no interventions were carried out.

A pro forma sheet to be filled out partially at ward of MCVTC with a detailed history including chief complaints, past and present medical and surgical history, vitals, body mass index (BMI) were obtained and later the tests on blood samples were carried out.Fasting blood samples were drawn and collected. Upon arrival at the laboratory within two hours, the blood samples were centrifuged at 4000 rpm for five min, aliquot was stored at -4^{o}C until analysis. Serum glucose (fasting) to screen for any new cases of diabetes mellitus, total cholesterol (T-C), triglyceride (TG), low density lipoprotein –cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) to check dyslipidemia, and serum total testosterone (TT) were measured. The serum concentrations of glucose, T-C, TG and HDL-C were measured by fully automated analyzer, BT 3000, Italy, in the clinical biochemistry laboratory. The autoanalyzer uses spectrophotometric technique to calculate the absorbance values and then measure the concentration of the analytes in the serum. The assay reagent along with the calibrators and controls were supplied by the reagent company in the same pack. TT was measured using the fully automated Enhanced Chemiluminiscent Immunoanalyzer, Ortho Clinical Diagnostics, Johnson and Johnson Company.

ECHO report of the patient that was done after/before admission, as a part in his/her management, within one week of blood sample collection was recorded. Transthoracic two-dimensional echocardiographic assessment was performed by experienced cardiologist via Vivid 7 system (GE Medical System) with 2.5-5 MHz probes.Coronary angiography was done through right radial artery approach using sheath size 5F, catheter Tiger 5F or JL4/JR4 and contrast omnipaque 100ml.

Severity of coronary stenosis in patients was estimated by the Gensini coronary score.[7] The Gensini score equals the sum of all segment scores (each segment score equals segment weighting factor multiplied by a severity score). The scoring is done as score 1 for 1-25% narrowing; 2 for 26-50% narrowing; 4 for 51-75% narrowing; 8 for 76-90% narrowing; 16 for 91-99% narrowing; 32 for total occlusion. The obtained score was then multiplied by a factor ranging from 0.5-5, depending upon the position of the lesion in artery involved. For example: 5 for the left main coronary artery, 2.5 for the proximal left anterior descending (LAD) or, left circumflex (LCX) coronary artery, 1.5 for the mid-LAD and 1 for the distal LAD, mid-distal LCX or right coronary artery0.5 for any other arteries

Operational Definitions: BMI - Height and weight were measured, and body mass index (kg/m^2) was calculated; Diabetes mellitus - Diabetes was considered present if the participant is under treatment with insulin or oral hypoglycemic agents, or the diagnosis is made according to the recommendations given by American Diabetic Association by measuring the serum glucose.[8]; Hypertension -is diagnosed if the patient is on antihypertensive drug treatment or if the blood pressure falls in the range of hypertension according to JNC-VII definitions.[9]

Statistical Analysis was performed using IBMSPSS (Statistical Package for Social Science) software version 20.0. Analyses included standard descriptive variable summaries, measures of distribution with frequency tables and quantitative variables expressed in terms of mean ± SD (Standard Deviation). Scale variables (Quantitative) were tested for statistical significance using Pearson's Correlation and values of "*p*" less than 0.05 were considered statistically significant. Mean values of study variables were also compared between and within categories using Analysis of Variance for Continuous variable and Chi-square test for the categorical variables and values of "*p*" less than 0.05 were considered significant measures of association between the variable.

RESULTS

The average ageof the 102 patients was 60.42 years with maximum people (30.4%) falling in between the range of 51-60 years. Majority of the patients (67.6%) were smokers and 45.1% consumed alcohol. In addition, 63.7% (65)of themwere hypertensive and 40.2% (41) of the patients were diabetic. Of the total CAD patients, 97 (95.1%) were on lipid lowering agent. Table 1 illustrates the baseline clinical characteristics of the patients with CAD which included blood pressure, BMI and other biochemical parameters.

In this study, majority of patients had normal (96.1%) left main coronary artery, the most common vessel to be stenosed was left anterior descending artery (82. 4%). Of the total 102 patients enrolled in the study, 31 (30.48%) had Single vessel disease, 29 (28.4%) had double vessel disease and majority of them 42 (41.2%) had triple vessel disease. Furthermore, the study findings also disclosed that out of 102 patients, major portion of the patient (46.1%) had normal ejection fraction of the left ventricle. Likewise, 28 (27.5%), 24 (23.5%) and 3 (2.9%) of them had mild, moderate and severe left ventricle ejection fraction respectively.

CVD risk factors like age, BMI, triglycerides and total cholesterol were found to be negatively correlated with testosterone level but not statistically significant as depicted in Table 2.

Table 1. Base line characteristics of patients.

	Mean ± SD*	Range
Age	60.42 ± 11.11	32 - 87
Systolic Blood Pressure	125.80 ± 14.62	90 - 160
Diastolic Blood Pressure	80.61 ± 9.30	60 - 110
Mean Arterial Pressure	95.67 ± 10.39	70 - 127
BMI	23.59 ±2.69	18 - 33
Random Blood Sugar (mg/dl)	138.79 ± 86.14	70 - 594
Total cholesterol (mg/dl)	146.01 ± 41.35	65 - 278
Triglycerides (mg/dl)	154.36 ± 95.72	55 - 770
HDL- C† (mg/dl)	31.22 ± 13.54	8 - 114
LDL- C‡ (mg/dl)	52.35 ± 33.93	57 - 158
Total testosterone (nmol/L)	12.01 ± 6.1	2.57 - 25.99

SD* Standard Deviation, HDL-C† High-density lipoprotein Cholesterol, LDL-C‡ Low-density lipoprotein Cholesterol

Table 2. Correlation between total testosterone and cardiovascular risk factors.

Variable of Interest	Pearson Correlation Coefficient (r)	p-Value
Age (yrs.)	-0.156	0.122
Mean Arterial Pressure	0.119	0.24
Body Mass Index (BMI)	-0.041	0.688
Random Blood Sugar (mg/dl)	0.019	0.854
Triglycerides (mg/dl)	-0.137	0.173
Total- Cholesterol (mg/dl)	-0.023	0.82
HDL- Cholesterol (mg/dl)	0.086	0.394
LDL- Cholesterol (mg/dl)	0.113	0.264

** For significant at 0.01 and * for significant at 0.05 level of significance

Negative correlation (r = -0.069) was found between Gensini score and TT but was not statistically significant (p=0.496). Similarly, when TT was compared with the number of vessel stenosed, as the number of vessel involved increased from 1 vessel disease (VD) to 2VD to 3VD, TT level dropped from 13.68 to 11.00 nmol/L but was not statistically significant (p = 0.17) as depicted in Figure 1.

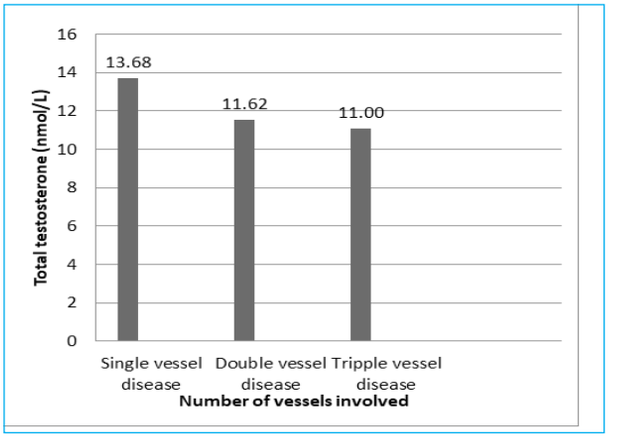

Figure 1. Mean comparison of testosterone levels with single, double and triple vessel disease.

The study findings revealed that while comparing the traditional risk factors and Gensini score with the different tertile group of testosterone, the values were found to be similar between the groups. But the proportion of diabetic patients differed significantly between the groups (P-value= 0.040) with highest percentage of diabetic patient in the lowest tertile group (Table 3).

Table 3. Baseline characteristics of patients by tertile group of testosterone.

	Tertile 1	Tertile 2	Tertile 3	
	<8.7 nmol/L (n=33) (Mean/n ± SD)	8.7- 12.7nmol/L (n=33) (Mean/n ± SD)	> 12.7 nmol/L (n=36) (Mean/n ±SD)	p-Value
Age (years)	61.55 ± 9.73	59.88 ± 11.78	60.18 ± 12.08	0.814
Mean Arterial Pressure	92.95 ± 9.81	96.57 ± 9.52	97.10 ± 11.70	0.214
Body Mass Index	23.29 ± 2.97	24.21 ± 2.61	23.35 ± 2.52	0.309
Random Blood Sugar (mg/dl)	144.00 ± 75.00	137.88 ± 72.22	137.44 ± 109.67	0.943
Total Cholesterol (mg/dl)	146.67 ± 43.77	149.06 ± 45.96	142.07 ± 40.94	0.81
Triglycerides (mg/dl)	158.61±77.05	176.91± 130.11	130.53 ±68.21	0.14
HDL Cholesterol (mg/dl)	30.86 ± 18.08	29.70 ± 12.96	33.36 ± 8.475	0.537
LDL Cholesterol (mg/dl)	49.66±38.99	50.39 ± 6.20	56.21±25.66	0.686
Gensini Score	35.67 ± 24.89	38.03 ± 29.35	34.18 ± 30.43	0.855
Ejection Fraction (Left Ventricle)	47.12 ± 14.41	48.88 ± 11.09	49.35 ± 13.08	0.76
Diabetic (%)	47.5	27.5	25	0.040*
Smoker (%)	29.4	38.2	32.4	0.251
Alcohol Consumer %	32.6	32.6	34.8	0.988
Hypertensive %	27	39.7	33.3	0.123

Values are expressed as mean ± SD. Continuous outcome variables were examined using ANOVA and categorical variables were examined using Chi-square test.

DISCUSSIONS

Men were always considered to be at higher risk than women for CAD. But recent studies have shown that testosterone has a cardioprotective role.[4,5,10] This has been the topic of debate in the recent years so this study tried to find the relation between testosterone and risk factors of CAD along with its relation with severity of disease.

The first aim of this study was to see the relationship between TT and total cholesterol, LDL-C and HDL-C and triglycerides. Earlier studies have shown both positive[11] and negative[12] correlation between TT and HDL-C and negative correlation between TT and total cholesterol, LDL-C and triglycerides.[11] This study did not find any correlation between total testosterone and lipid profile and this lack of correlation may be partially attributed to the use of statin as maximum number of the patients are under this medication. Statin is a hydroxy-methylglutaryl-coenzyme A reductase inhibitor (HMG CoA) which reduces plasma cholesterol, LDL-C and triglyceride.[13]

Secondly, this study aimed at finding the relation between severity of CAD and TT. Initially, when the scoring system was not developed, severity was assessed by simply defining single-, double-, triple-vessel and left main disease, with luminal stenosis of either ≥50 or ≥70%. From then on, different scoring system came into use like Gensini, Coronary Artery Surgery Study, Syntax scoring system etc. and out of these the most commonly used one is the Gensini score system.[14] This study also used the Gensini scoring system along with number of vessels involved for the assessment of severity of disease. But no association was found between TT and the Gensini score and with the number of vessels. The reason behind this may be the cross-sectional nature of this study and also the cases were not compared with the control group but only compared among the different tertile of testosterone. There are many similar case-control studies that have found no association between androgen level and CAD in men[15] supported by many prospective studies.[16] But at the same time there are several cross-sectional and prospective studies which have shown controversial results. The possible reasons for this may be lack of measurement of free and bioavailable testosterone which have shown strong association with CAD.[17, 18]

Obesity may have a role in causing low testosterone level. Both cross-sectional[19] and longitudinal studies[20,21] have confirmed that abdominal adiposity is inversely linked with testosterone levels. In this study, the BMI of most of the patients were within the normal range and this may the reason behind the lack of correlation

between testosterone and BMI.

Multiple large studies have shown that low level of testosterone was associated with diabetes and were found to have statistically low levels even after adjustment for obesity and fat distribution.[22, 23] Similar result was obtained in this study. With the increasing tertile of testosterone, the number of diabetic patients gradually decreased. But from this cross-sectional study, it is not possible to establish the cause and effect relationship. In a cross-sectional study, 53 nondiabetic men were taken out of which 18 had prostrate carcinoma (PCa) and received androgen deprivation therapy (ADT) 12 months prior to the study, 17 with PCa but without ADT and remaining 18 were age-matched controls. The result showed that men with PCa receiving ADT were at higher risk of developing insulin resistance and hyperglycemia as compared to others.[24] In another prospective study, testosterone replacement was tried in hypogonadal men with type 2 diabetes mellitus and followed for 12 months. The result showed a significant improvement in glycemic control.[25] Testosterone is known to cause decrease fat accumulation, decrease differentiation of fat cell precursors and increase lipolysis[26] which may have caused improvement in glycemic control. But on the other hand, insulin seems to stimulate hypothalamus to release gonadotropin releasing hormone, which consequently results in increase testosterone production.[27] So it can be argued that decreased stimulation of the hypothalamus in diabetics secondary to lack of insulin action could result in decrease testosterone level.

CONCLUSIONS

This study suggests that low testosterone is associated with diabetes mellitus which is a risk factor for CAD, however, cannot strongly agree or disagree with negative relation between serum testosterone and CAD, and thus warrants further investigation.

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