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A STUDY OF CLINICAL PROFILE OF ACUTE CORONARY SYNDROME AND ITS CORRELATION WITH SERUM FREE TESTOSTERONE LEVEL IN MEN IN TERTIARY CARE HOSPITAL OF UTTARAKHAND

Cardiology

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ABSTRACT

Serum free testosterone has been extensively studied for its role as immunomodulatory effect, anti-inflammatory action and its favourable impact on lipid profile , blood pressure. Earlier higher levels of testosterone were thought to have deleterious effect on cardiovascular system, in last few years there has been studies suggesting low testosterone levels are associated with increase prevalence of cardiovascular disease. Aims & Objectives:1. To estimate s. free testosterone level in male patient suffering acute coronary syndrome(ACS). 2.To correlate the association of s. free testosterone level with pattern of ACS. 3.To correlate s. free testosterone level with mortality and morbidity in male patients presenting with ACS. **Material & Methods:** Source: This study was carried out in tertiary hospital of Uttarakhand included 100 case and 25 controls. Diagnosis of ACS was confirmed by ECG, troponin I and CAG in each case. A baseline serum Free Testosterone level was evaluated at the time of admission. **OBSERVATION:** Mean age in case and control was 48.24±10.84 and 46.88±10.94 years respectively. Mean BMI 23.5±2.62 and 22.9±3.26kg/m2 respectively. Low serum free testosterone levels were found in 61% of cases and 8% of control group. Difference of serum free testosterone levels among cases and controls was found to be statistically significant ($p<0.05$). We found significantly Low serum free testosterone in different types of ACS viz STEMI, NSTEMI and Unstable Angina as compared to control. ($p<0.05$). We also tried to correlate serum free testosterone levels with different lipid parameters but the difference among the groups was insignificant.
Conclusion: s. free testosterone levels were significantly low in patients with ACS as compared to control. Mean serum free testosterone were lower in STEMI group as compared to NSTEMI though the difference was statistically insignificant, however it did not show any correlation with the pattern of myocardial infarction.

KEYWORDS

Acute Coronary Syndrome, serum free testosterone, STEMI,NSTEMI, UA.

INTRODUCTION:

Acute coronary syndrome (ACS) is a major cause of mortality and morbidity in the Asia-Pacific region and account for around half of the global burden from these conditions that is around seven million deaths and 129 million disability-adjusted life years. Myocardial infarction and future cardiovascular risks are higher among men than women; this difference appears to be eliminated in the last decade as men show a decrease with corresponding female increased mortality associated with coronary artery disease still men are more than twice as likely to develop CAD. [1-3]

The management of acute coronary syndromes varies widely between countries in Asia. In this area, hospital admission can create significant financial hardships for participants as treatment costs in many settings are borne largely out of pocket. Though coronary angiography and revascularization is the gold standard in management of ACS but this is not available to a large subset of patients so there is need to search different surrogate marker and additional medical management which can improve outcome in patients presenting with ACS.[4]

Acute coronary syndrome results from disturbed normal function of vascular endothelium (influenced by various risk factors high level LDL, low HDL, cigarette smoking, hypertension, diabetes etc.). These functions include local control of vascular tone, maintenance of antithrombotic surface, and control of inflammatory cell adhesion and diapedesis. Loss of these defence leads to inappropriate constriction, luminal thrombus formation, and abnormal interaction between blood cells especially monocytes and platelets and the activated vascular endothelium which ultimately leads to atherosclerotic plaque formation, plaque rupture or erosion of cap leads to platelet aggregation and deposition of fibrin strands which traps the RBCs and thrombus formation take place obstructing the distal flow lead in to acute coronary syndrome. Inflammation plays an important role in the initiation and progression of atheromatous plaque formation and its clinical consequences. Cytokines are the mediators of cellular inflammation and promote local inflammation in the arterial wall, which may lead to vascular smooth muscle apoptosis, degradation of the fibrin cap and plaque rupture. Recent studies have suggested that cytokines are pathogenic in contributing directly to the disease process. Testosterone has been shown to have immuno-modulating effects, and appears to suppress activation of pro-inflammatory cytokines. An anti-inflammatory effect of normal physiological levels of sex hormones may therefore, be important in athero-protection. Ikonomidis et al, 1999 has shown patients with CAD have elevated circulating levels of cytokines and C-reactive proteins (CRP). Manten et al 1998 have shown cytokine like IL-6, Fibrinogen peptide A as an independent predictive marker in Acute Myocardial Infarction and Unstable Angina.[5-7]

Cytokine activation and vascular smooth muscle cell apoptosis play an integral part in the development of CAD and in the pathophysiology of acute coronary syndrome. Testosterone has been shown to suppress pro-inflammatory cytokine activity, inhibit apoptosis and enhance vascular smooth muscle cell proliferation. This action may be responsible for its atheroprotective effects (Journal of Endocr, 2003). Testosterone could, therefore, potentially be involved in maintaining fibrous cap of the atherosclerotic plaque by promoting smooth muscle cell stability. [5]

In this study we have taken the male patients in order to correlate the role of serum free testosterone level in patients with Acute Coronary Syndrome. This study is significant because of the fact the, majority of

subject with ACS are unable to utilize the gold standard investigation coronary angiography as either it is not available or it creates a financial burden on the patients so there is need for non-invasive marker which can be used as a predictive marker for ACS.

AIMS AND OBJECTIVES

- To estimate the level of free testosterone level in male patient suffering acute coronary syndrome.
- To correlate the association of free testosterone level with pattern of acute coronary syndrome.
- To correlate free testosterone level with mortality and morbidity in male patients presenting with acute coronary syndrome.

MATERIAL AND METHOD:

Source:

This study has been carried out in the Department of internal medicine in Sri Guru Ram Rai Institute of medical and Health Sciences and Sri Mahant Indresh Hospital (SMIH) Dehradun. This is a cross sectional study and we have included male subjects presenting with Acute Coronary syndrome.

An informed written consent from the patient or legal guardian was taken in all the patients included in the study.

A detailed history and examination was done on all patients suspected with cardiogenic chest pain. Baseline ECG and Cardiac Biomarker (Trop I, CPK MB) and other relevant investigations (ECHO, TMT, Coronary Angiography etc.) as per the requirement was done in each patient to confirm the diagnosis. A baseline serum Free Testosterone [ELISA METHOD] level was taken at the time of admission.A total of 100 cases Age & sex matched healthy controls [No 25] were taken from the medical ward or OPD reporting for executive investigations excluding the patients having conditions responsible for low testosterone levels. Study has been carried out between Oct 2015 and Sep 2017.

SERUM FREE TESTOSTERONE (ELISA Method)

Principle

Free Testosterone (antigen) in the sample competes with the antigen conjugated with horseradish peroxidase (HRP) for binding to the limited number of anti-testosterone antibodies on the microplate (solid phase). After incubation the bound/free separation is performed by a simple solid-phase washing. Finally, the enzyme in the bound-fraction reacts with the Substrate (H2O2) and the TMB Substrate and develops a blue colour that changes into yellow when the Stop Solution (H2SO4) is added. The colour intensity is inversely proportional to the Free Testosterone concentration in the sample. Free Testosterone concentration in the sample is calculated through a calibration curve.

Inclusion criteria:

Male patients presenting with acute coronary syndrome between the age group of 18 - 65 years.

Exclusion criteria:

- Patient with liver disease
- Patient with renal parenchymal disease
- Patient with diabetes mellitus

Statistical analysis:

In the present study the data obtained has been analysed using statistical methods. Mortality profile and Morbidity profile has been studied along with the comparison between cardiac biomarker, pattern and type of ACS and serum free testosterone levels.

RESULTS:

Table- 1

Base line characteristics among the cases and control

Characteristics	Cases(n=100)	Controls(n=25)
MEAN AGE(years)	48.24±10.84	46.88±10.94
BMI (kg/m^2)	24.12±2.5	24.45±2.71
SBP(mmHg)	127±19.74	126±10.23
DBP(mmHg)	77.15±13.85	73.28±7.18
SMOKER	59%	30%
ALCOHOLIC	31%	25%
HTN	17%	10%

Table -2

Clinical Profile of patients with STEMI and NSTEMI with normal testosterone levels and their comparison with Control (N=25)

	STEMI (cases with normal s free testosterone)	NSTEMI (cases with normal s free testosterone)	Controls
MEAN AGE (years) N=26	47.46±11.4	45±10.44	46.88±10.94
MEAN TESTOSTERONE (pg/ml) N=26	6.76±2.63	7.28±3.67	10.11±4.87
MEAN TROP I(ng/ml) N=12	4.39±3.62	2.20±3.48	N/A
LIPID PROFILE (N=21)	4.95±1.55	5.2±1.28	5.06±1.37
MEAN LDL(mg/dl) MEAN TOTAL CHOLESTROL : HDL	86.29±38.87	99.23±42.53	105±44
MEAN TRIGLYCERIDE (mg/dl)	140.06±81.7	138.18±79.97	131.39±66.66
MEAN DURATION OF STAY(days) (N=26)	4.26±1.88	2.83±1.64	
ECG PROFILE IWMI AWMI ALWMI	9 13 4	3 9 0	

Table -3

Clinical Profile of patients with STEMI and NSTEMI with low testosterone levels and their comparison with Controls (N=25)

	STEMI (cases with low s free testosterone)	NSTEMI (cases with low s free testosterone)	Controls
MEAN AGE(yrs) N=38	49.57±10.05	48.94±12.06	46.88±10.94
MEAN TESTOSTERONE (pg/ml) N=38	2.43±0.7	2.57±0.8	10.11±4.87
MEAN TROP I(ng/ml) N=15	3.26±3.76	1.17±2.72	
LIPID PROFILE (N=32)	4.93±1.96	4.96±1.62	5.06±1.37
MEAN TOTAL CHOLESTROL : HDL MEAN LDL(mg/dl)	103.32±48.86	102.12±35.14	105±44
MEAN TRIGLYCERIDE(mg/dl)	115.89±15.14	122.42±48.87	131.39±66.66
MEAN DURATION OF STAY(days) N=38	3.52±2.3	4.21±2.71	
ECG PROFILE IWMI AWMI ALWMI	16 3 19	3 13 3	

Table -4 A
Comparison of mean Serum Free Testosterone levels among Cases and Controls

	N	Mean Serum Free Testosterone Levels (pg/ml)	P VALUE
CASES	100	4.21±2.87	<0.05
CONTROLS	25	10.11±4.87	

Table – 4B
Serum free testosterone level and coronary artery disease (ACS) cross tabulation

S. free testosterone	Cases (ACS)	Controls (without ACS)
< 3.84 pg/ml	61	2
> 3.84 pg/ml	39	23

Corrected Chi-square test : 20.4033; Risk ratio (95% CI) : estimated 1.5393 (Lower- 1.2649; upper- 1.8732). Odds ratio (75% CI) :estimated-17.9872 (Lower- 4.0144; Upper- 80.5943)

p value = 0.000001 significant
In the present study group, the normal level of serum free testosterone is 3.84-34.17 pg/ml.

In the case group, 61 patients (61%) had serum free testosterone level lesser than 3.84 pg/ml while in control group only 2 subjects had lesser than 3.84 pg/ml. Serum free testosterone level is significantly decreased in patients who had acute coronary syndrome.The sensitivity of the test is 61%.

Table – 5
Mean serum free testosterone level comparison among different type of ACS

ECG	N	MEAN FREE TESTOSTERONE(pg/ml)	Mean S testosterone level among control(N=25)	P value
STEMI	64	4.19±2.76	10.11±4.87	<0.05
NSTEMI	31	4.39±3.28	10.11±4.87	<0.05
UA	5	3.45±3.28	10.11±4.87	<0.05

Table – 6
Mean serum free testosterone level comparison among different patterns of ACS

	N	FREE TESTOSTERONE LEVEL	Mean S testosterone level among control(N=25)	P VALUE
AWMI	54	4.28±2.93	10.11±4.87	<0.05
IWMI	31	4.45±3.20	10.11±4.87	<0.05
ALWMI	10	3.52±1.90	10.11±4.87	<0.05

Table - 7
Comparison of Serum free Testosterone with different lipid parameters

Free Testosterone level (pg/ml)	Total Cholestrol level(mg/dl)	Mean S. TGs (mg/dl)	Mean LDL levels	Mean HDL levels (mg/dl)	P valvue
Low (n=57)	157.0±50.09	114.77±50.77	100.52±43.72	34.42±11.07	>0.05
Normal (n=53)	158.3±46.64	138.41±75.81	97.08±42.30	31.69±7.89	

Table – 8
Correlation of S free testosterone levels with in hospital mortality

S free testosterone	Mortality	
Low	1	100%
Normal	0	0%

Only one patient expired among the case belonging to low s free testosterone group with STEMI.

DISCUSSION:

The present study has been conducted in the department of Internal Medicine of SGRRIM&HS to study the clinical profile of ACS and its correlation with serum free testosterone level in tertiary care hospital of uttarakhand.

In this study there are 100 cases of ACS and 25 controls. Mean age in this study is 48.24± 10.84 years among the cases and 46.88±10.94 years among the controls. Mean BMI in our study in case group and control group is 24.12±2.50 kg/m^2 and 24.45±2.71 kg/m^2 respectively. Whereas in the study done by GMC Rosano et al , mean BMI was 26.20±3.10 kg/m^2 and in K M English et al study it was 27.7±0.7 kg/m^2.[8,9]

In this study S free testosterone level in patients with ACS has been found significantly low in 61% cases (Table 4B). Similar observations were found by G B Phillips et al. Hak et al also found the low levels of the endogenous androgens are associated with increased risk of artherosclerosis. English et al in 2000 concluded in their study that men with CAD has significantly low level of free testosterone. Allmeh et al in 2005 also demonstrated similar results showing significantly low testosterone and DHEAS levels in patients with CAD.[9-11]

We had only one patient in Hospital mortality in low testosterone group with STEMI(table-8). K T Khaw et al in 2007 concluded that testosterone levels are inversely related to mortality due to cardiovascular disease.[12]

Thus our study indicates a negative correlation of serum free testosterone level with ACS.so low serum free testosterone level can serve as risk predictor for ACS, further randomized control trails showing the effect of testosterone replacement in ACS patients may shed more light on its role in pathogenesis of ACS.

CONCLUSION:

- The serum free testosterone was found to be lower in patients with acute coronary syndrome as compared to controls. The difference between cases and controls was statistically significant. (P< 0.05)
- The serum free testosterone levels were also significantly low in the all type and pattern of ACS as compared to controls,
- We could not find any significant difference in Serum free Testosterone levels among the different types and pattern of ACS.
- No correlation was found between serum free testosterone level and in hospital mortality and morbidity in patients with acute coronary syndrome.
- Serum free testosterone levels correlation with different lipid parameters was found to be insignificant in our study.

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