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Study of Acute Coronary Syndrome in Premenopausal Women in Correlation with Sex Hormones

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ABSTRACT

Objectives: Higher testosterone and lower Estrogen levels are associated with cardiovascular disease in women. However, studies on endogenous sex hormones and acute coronary syndrome (ACS) in pre-menopausal women are sparse.

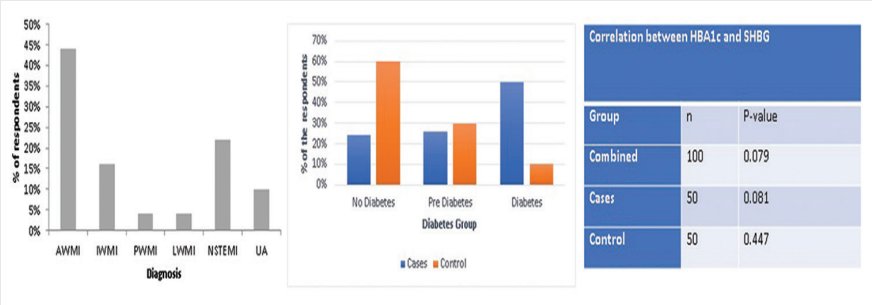
Material and Methods: We studied 50 pre-menopausal women presenting with ACS and age-matched controls who consented to the study with Testosterone, Estradiol, and Sex hormone-binding globulin (SHBG) levels at baseline. They were clinically followed up for 6 months duration.

Results: The mean age was 37.42 ± 5.7 years. 48% patients were obese. The mean body mass index was 27.53 ± 5.41 kg/m^2. Hypertension followed by Diabetes was the most common risk factor. 14% had family history of coronary artery disease (CAD). 24% had atypical chest pain at presentation. Anterior wall ST elevation myocardial infarction was the most common presentation. Single-vessel disease was seen in 38%; 24% had Non-Obstructive CAD. Ratios of Bioavailable Testosterone: Estradiol, Estradiol: Low-density Lipoprotein (LDL), Estradiol: High-density Lipoprotein, SHBG: LDL, and SHBG: HbA1c were analyzed in cases and controls and were not found to be significantly associated.

Conclusion: Endogenous sex hormones were not found to be significantly associated with ACS in premenopausal women.

Keywords: Acute coronary syndrome, Endogenous sex hormone, Premenopausal women,

ABSTRACT IMAGE



INTRODUCTION

A leading cause of death is coronary artery disease (CAD) in women.[1] There are specific differences in the prevalence of CAD with respect to gender. CAD risk increases in women after menopause.[2] Higher androgen and lower levels of endogenous estrogen that occurs after menopause may result in an increased CAD risk in postmenopausal women.[2,3] The altered hormonal milieu in postmenopausal women is associated with CAD risk factors, such as insulin resistance, high C-reactive protein, and high blood pressure.[5-7] In MESA study, an elevated risk for heart failure and cardiovascular disease (CVD) was seen in patients with a higher ratio of serum testosterone to estradiol.[4]

Higher risk for CAD was seen in women with higher total testosterone levels and higher estradiol levels were associated with a lower risk of CAD. Women's Health Initiative, Heart and Estrogen-Progestin Replacement Study 2 (HERS2), and HERS studies do not support the beneficial vascular effects of hormone replacement therapy in postmenopausal women.[8,9] Receptors for estrogen, progesterone, and testosterone are expressed in endothelium and vascular smooth muscle of multiple vascular systems.[10,11] It is one of the proposed mechanism responsible for gender difference in vascular tone.

Increased serum prolactin levels are associated with major depressive disorder especially in women. There is an increased risk of developing cardiometabolic disease in major depressive disorders. Physiologically, prolactin has a role in the regulation of stress, anxiety, and weight gain. Dysregulation of neuroendocrine axis in major depressive illness may extend to this hormone.[12]

Very few studies have examined the role of endogenous sex hormones and CAD in the premenopausal age group. There is an increasing trend of premenopausal women presenting with acute coronary syndrome (ACS). This study was funded by Rajiv Gandhi University of Health Sciences, Bengaluru.

MATERIALS AND METHODS

Fifty consecutive patients with ACS in the premenopausal age group who consented to the study were included in the study. Age-matched controls were taken. Clinical, demographic, and treatment details were recorded. Three months clinical and telephonic follow-up was done post-discharge. The concentrations of sex hormones were measured from fasting serum samples drawn at the baseline between 7:30 AM and 10:30 AM. It was stored at −70°C until analysis. Radioimmunoassay kits were used to measure total testosterone levels. Sex hormone-binding globulin (SHBG) was measured using a chemiluminescent enzyme immunometric assay. Estradiol was measured using an ultra-sensitive radioimmunoassay kit. Concentrations of bioavailable testosterone (the sum of SHBG-bound and albumin-bound Testosterone) and free testosterone (reported as a percentage of total Testosterone) were calculated.[14] Total testosterone/estradiol ratio was calculated for each participant. Serum prolactin levels were assayed.

Statistical method used

The data were analyzed using Microsoft Excel and R-4.1.0 software. All the tests of significance were carried out at 5% level of significance. The descriptive results displayed as subgroups of cases and controls. The numerical data are presented as mean and standard deviations. All the categorical data are presented in the study as frequency and percentages. Descriptive statistics is used for frequency tables, summary statistics and inferential statistics for independent sample *t*-test were used.

RESULTS

Most patients were in the 31–40 years age group [Table 1]. The mean age was 37.42 ± 5.7 years. About 48% were obese. The mean body mass index was 27.53 ± 5.41 kg/m^2. There were

no patients in study group who consumed alcohol or tobacco in any form. Hypertension followed by diabetes was the most common risk factors. About 14% had a family history of CAD. About 24% had atypical chest pain at presentation and 22% had presyncopal symptoms. ST-segment elevation myocardial infarction (STEMI) was the most frequent presentation with anterior wall MI being the most common [Figure 1]. About 48% had mild LV systolic dysfunction and 84% of patients were in Killip's class I at presentation. About 90% of patients underwent angiogram; single-vessel disease was seen in 38% and left anterior descending artery was the most common vessel involved; and 24% had non-obstructive CAD.

About 26% had pre-diabetes and 50% had diabetes in the cases group [Figure 2].

About 56% had anemia and 98% had low-density lipoprotein (LDL) levels greater than 70 mg/dl. The mean LDL was 104.44 ± 18.59 mg/dl. The mean high-density lipoprotein (HDL) was 39.32 ± 4.37 mg/dl. About 78% had high triglyceride levels. The mean triglycerides were 175.28 ± 74.79 mg/dl. There were marginally higher levels of serum prolactin levels in cases than in controls – 17.78 ng/ml versus 14.85ng/ml. The total testosterone to estradiol ratio showed an inverse relationship in cases with a positive trend but was not statistically significant. When bioavailable testosterone: estradiol levels were analyzed, it was not found

Table 1: Clinical and demographic profile.

Variables	n (%)
Age	
20–30 years	2 (4%)
31–40 years	26 (52%)
41–50 years	22 (44%)
BMI (kg/m^2)	
<18.5	2 (4%)
18.5–24.9	24 (48%)
25–29.9	18 (36%)
30–39.9	6 (12%)
Risk factors	
Diabetes	21 (42%)
Hypertension	26 (52%)
Family history	7 (14%)
COPD	3 (6%)
Hypothyroid	2 (4%)
Previous IHD	15 (30%)
Anemia	9 (18%)
Symptoms	
Chest pain	36 (72%)
Typical	24 (48%)
Atypical	12 (24%)
Dyspnea	20 (40%)
Fatigue	38 (76%)
Palpitation	3 (6%)
PND	9 (18%)
Orthopnea	9 (18%)
Back ache	15 (30%)
Pre-syncope/syncope	11 (22%)
Diagnosis	
AWMI	22 (44%)
IWMI	8 (16%)
PWMI	2 (4%)
LWMI	2 (4%)
NSTEMI	11 (22%)
Unstable angina	5 (10%)
EF%	
<30 Severe	0
30–40 Moderate	2 (8%)
40–50 Mild	24 (48%)
>50 Adequate	22 (44%)
KILLIPs class	
Class I	42 (84%)
Class II	6 (12%)
Class III	2 (4%)
Class IV	0
CAG	45 (90%)
SVD	19 (38%)
DVD	10 (20%)
TVD	4 (8%)
Non-obstructive CAD	12 (24%)
PTCA	20 (40%)

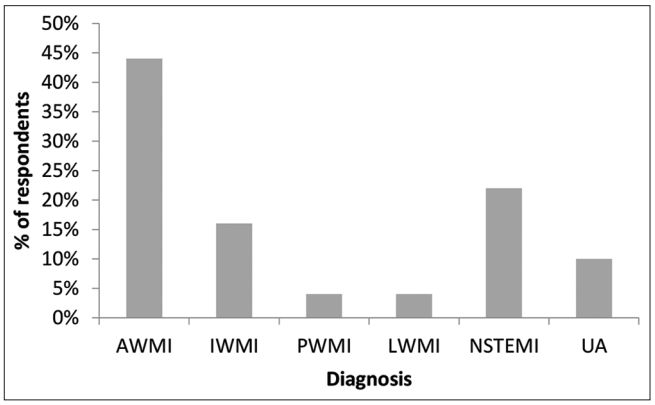


Figure 1: Percentage distribution of type of MI in the study group.

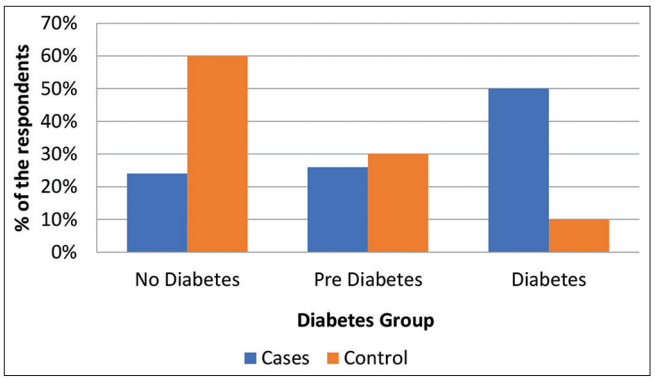


Figure 2: Percentage distribution of patients based on glycemic status.

Table 2: Endogenous sex hormones and test of significance between cases and control.

Variables	Group	*n*	Mean	Standard deviation	*t*-test value	df	*P*-value	Conclusion
Total Testosterone: Estradiol	Cases	50	0.2992	0.2264	1.794	98	0.076	Not Significant
	Control	50	0.4072	0.3698				
Bioavailable testosterone: Estradiol	Cases	50	0.1354	0.1276	1.156	98	0.251	Not Significant
	Control	50	0.1699	0.1680				
Estradiol: LDL	Cases	50	0.0013	0.0013	1.269	98	0.208	Not Significant
	Control	50	0.0017	0.0017				
Estradiol: HDL	Cases	50	0.0034	0.0031	1.295	98	0.198	Not Significant
	Control	50	0.0043	0.0042				
SHBG: LDL	Cases	50	0.4052	0.2449	0.970	98	0.335	Not Significant
	Control	50	0.4764	0.4576				
Follicular	Cases	26	81.335	12.9603	0.553	50	0.583	Not Significant
	Control	26	93.362	17.4682				
Luteal	Cases	24	101.925	83.9084	0.591	46	0.557	Not Significant
	Control	24	115.938	90.2985				

SHBG: Sex hormone-binding globulin, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 3: Correlation between HBA1c and SHBG.

Group	*n*	Correlation value	*P*-value	Conclusion
Combined	100	−0.176	0.079	Not significant
Cases	50	−0.249	0.081	Not significant
Control	50	−0.11	0.447	Not significant

Interpretation: Lower degree negative correlation, SHBG: Sex hormone-binding globulin

to differ in the two groups. Ratios of estradiol with LDL and HDL were not significant [Table 2]. The relationship between SHBG and HBA1c levels was not found to be significant [Table 3].

DISCUSSION

CAD increases exponentially after a woman attains menopause. It is said to be due to the wearing off of the protective effect of endogenous sex hormones.[13] Endogenous sex hormones have both genomic and non-genomic effects on endothelium and vascular smooth muscle. It was shown that women have a higher risk of death and heart failure than men in the 5 years following a STEMI even after accounting for differences in angiographic findings, revascularization, and other confounders in a large-scale cohort study.[14] In our study, there were no deaths documented in-hospital. One patient died on follow-up at 3 months for non-cardiac reasons.

Women with CAD characteristically have a higher prevalence of angina, greater comorbidities, and higher prevalence of non-obstructive CAD on angiography than men with CAD.[14,15] In our study, 42% and 52% had diabetes and hypertension, respectively. Prior ischemic heart disease was seen in 30% of cases. Non-obstructive CAD is known to predominantly affect postmenopausal women,[16] where estrogen is implicated in coronary microvascular dysfunction by modulating endothelial nitric oxide in vascular endothelium. In our study, non-obstructive CAD was seen in 24% of cases.

Low SHBG in postmenopausal women is a potential risk marker for cardiovascular and metabolic morbidity.[17] Low SHBG has been described as an independent predictor of incident type 2 diabetes,[18] reflecting a pre-diabetic state along with obesity, higher glucose, and insulin levels.[19-21] In our study, the ratio of SHBG with HbA1c was analyzed. There was no significant difference in the study and control group.

In postmenopausal women, extremely high concentrations of endogenous testosterone was associated with a high risk of ischemic heart disease and death and extremely low concentrations of endogenous estradiol was associated with a high risk of ischemic heart disease.[22, 23] Our study involved testing endogenous sex hormones only at baseline. There was no difference in the level of estradiol and testosterone between cases and controls. There, however, was an inverse relationship of testosterone to estradiol ratio in cases.

The menopause transitional period is associated with considerable increase in risk for CAD.[23, 24] Studies have shown that distinct alterations occur during menopause transition in endogenous sex hormones, adverse changes in body fat distribution, lipids, and lipoproteins and vascular health. About 44% of our patients were in the 41–50 years age subgroup, the menopausal transition group.

In the Framingham heart study, prolactin levels were not associated with incident CVD risk factors.[25] Higher levels of serum prolactin were seen in cases in comparison to controls in our study. The relevance of it is difficult to interpret in view of small sample size.

CONCLUSION

There was no relationship observed between endogenous sex hormones and acute coronary event in premenopausal women. In addition, whether plasma concentrations of sex steroids reflect the entire hormonal metabolism at the tissue level remains unclear.

Limitations of the study

The study involved small sample size. Serial testing of endogenous sex hormones was not done. The study subjects had only baseline testing.

Acknowledgment

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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