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Relationship between Serum Sex Hormones and Coronary Artery Disease in Premenopausal Women – A Missing Link?

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ABSTRACT

Objectives: The reported incidence of coronary artery disease (CAD) is on the upsurge in middle-aged women of 35–54 years, whereas decreasing in similar aged matched men. The current clinical trial studies have revealed that attention is drawn away from estrogens and shifted toward androgens and sex hormone-binding globulin considered potential mediators of increasing cardiovascular risk in women at midlife. Data evaluating the endocrinological basis for CAD in premenopausal Indian women is infrequent. We aimed to assess the incidence of CAD among premenopausal women undergoing coronary angiography, identify the prevalence of various risk factors for CAD, and compare clinical characteristics and hormonal levels among premenopausal women with and without CAD to elucidate endocrinological explanations for CAD in premenopausal women.

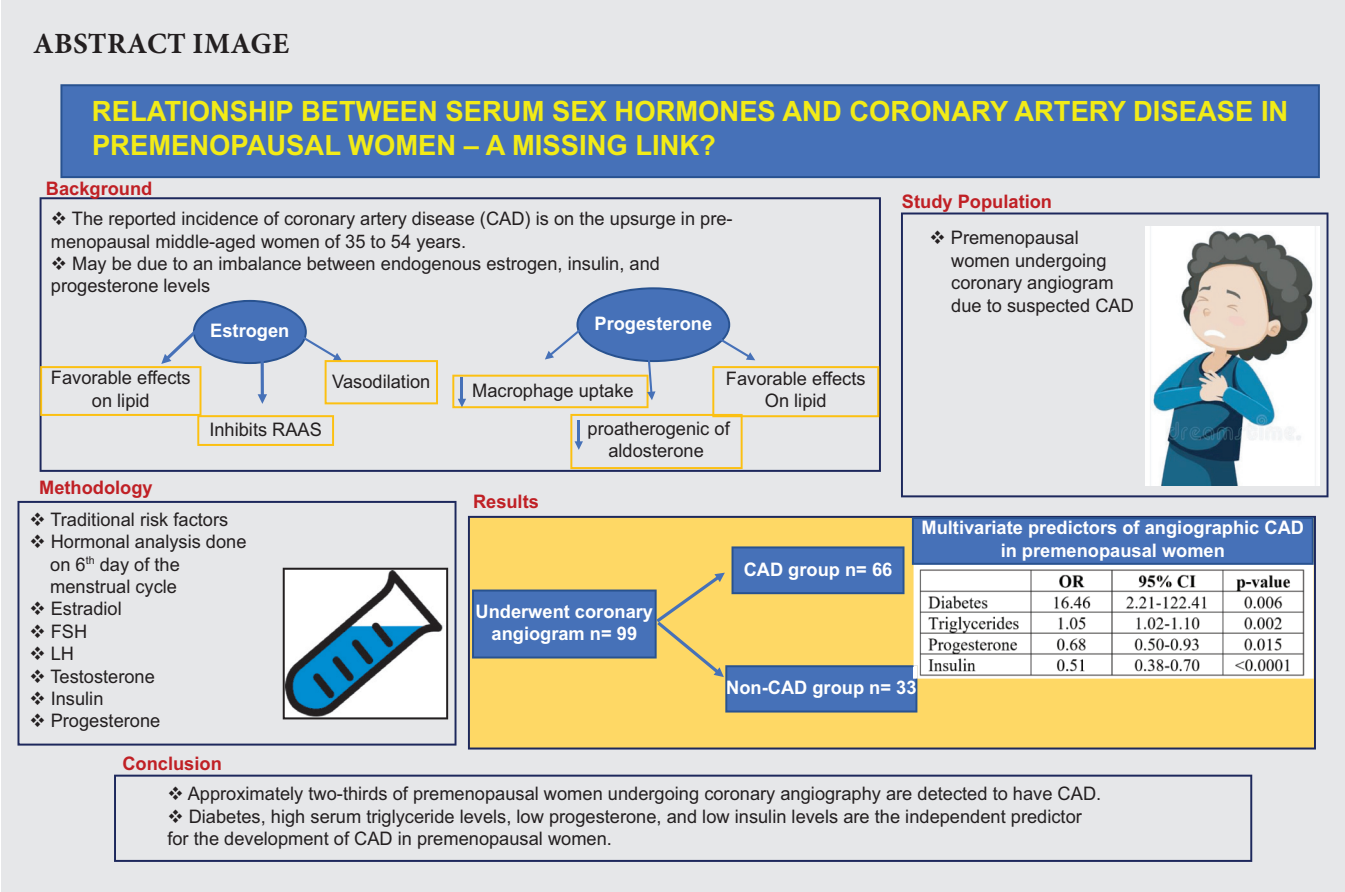
Materials and Methods: Ninety-nine consecutive premenopausal women undergoing coronary angiography between January 2014 and January 2017 were enrolled in this single-center and cross-sectional study. The reproductive hormone levels were quantified using commercially available electrochemiluminescence immunoassay.

Results: Sixty-six (66.7%) premenopausal women had CAD on coronary angiography. Multivariate linear regression analysis was used, for diabetes mellitus (adjusted odds ratio [AOR] 16.46; $P = 0.006$ [95% confidence interval, CI: 2.21–122.41]), triglycerides (AOR 1.05; $P = 0.002$ [95% CI: 1.02–1.10]), progesterone (AOR 0.68; $P = 0.015$ [95% CI: 0.50–0.93]), and insulin (AOR 0.51; $P < 0.0001$ [95% CI: 0.38–0.70]) were observed to independently anticipate the development of CAD in premenopausal women.

Conclusion: Approximately two-thirds of premenopausal women undergoing coronary angiography are detected to have CAD. Patients having diabetes, high serum triglyceride levels, low progesterone, and low insulin levels are considered in the high-risk category for developing CAD, thereby in premenopausal women providing a hormonal basis for the development of CAD.

Keywords: Coronary artery disease, Premenopausal women, Serum sex hormones

ABSTRACT IMAGE



INTRODUCTION

Studies have shown low incidence of coronary artery disease (CAD) among premenopausal women.[1] Despite recent data showing evidence that younger women presented with CAD have a poor prognosis as compared to age-matched men,[2] a significant dearth of facts available concerning risk factors, strategies for prevention, testing for diagnosis, and CAD treatment in women, particularly in the age group of the younger ones.[3] One of the studies done by Vaccarino *et al.*[4] revealed that among women aged <50 years, the mortality rate described for early myocardial infarction (MI) was reported more than twice that defined for age-matched men ($P < 0.001$, 6.1% vs. 2.9%; between the age and gender) but, on the evaluation of severity indicators of CAD, along with medical treatment regimens, could not freely explain the above-described difference in mortality. Extraordinarily, in premenopausal women incidence of MI is lower in comparison to same-age group men, this suggests a significant role for sex hormones in the etiology of MI.

There has been an ancient hypothesis that governs the fact that endogenous ovarian hormones compromise a protective effect on the occurrence of coronary heart disease (CHD). Women's Ischemia Syndrome Evaluation (WISE) study shows that young women represented with endogenous estrogen deficiency have increased risk in the coronary artery, that is, more than sevenfold.[5] Several metabolic factors such as lipids, inflammatory markers, and the coagulant system are regulated by estrogens. Through α- and β-receptors in the vessel wall promoted the direct vasodilatory effect. Smoking is the main risk factor that decreases the estrogen-dependent vasodilatation of the endothelial wall in young premenopausal women.[6] Previously published studies stated that an association of hormonal dysfunction with an increased risk of coronary events and atherosclerosis were observed in premenopausal women. In already published reports, it was described that an important section of the premenopausal women in the WISE study have shown profiles of reproductive hormone and symptoms compatible with hypothalamic hypoestrogenemia, frequently considered to be associated with amenorrhea and ovulatory cycles. Hypoestrogenemia of hypothalamic origin was characterized by disruption of ovulatory cycling and among premenopausal women of the WISE study reported to be mainly associated with angiographic CAD.[7]

Conversely, most of the clinical trials revealed that the risk of coronary disease does not reduce by hormone replacement

therapy in postmenopausal women,[8,9] suggestive that the main determining factor of enhanced cardiovascular disease (CVD) risk might be associated with the menopausal transition, but are not due to declining estrogen levels. Adverse cardiovascular (CV) risk factors in women categories of both premenopausal and postmenopausal are basically linked with androgens and sex hormone-binding globulin (SHBG),[10,11] with increased testosterone, and decreased SHBG that have shown a strong association with central adiposity, increased triglycerides, and decreased high-density lipoprotein (HDL) cholesterol levels. Higher rates of diabetes are mostly linked with low levels of SHBG. Mostly, an increase in CV risk factors and CVD events have been found to be linked with SHBG and the free androgen index (FAI).[12] Studies of women across the nation show that in women of the premenopausal category and in the early perimenopausal category, hormones involved, mainly low SHBG and high FAI, are also related to risk factors responsible for CVD. An interesting estrogen-androgen paradox phenomenon[13] exists to suggest that endogenous sex hormones may relate both to atherosclerotic CVD and its risk factors oppositely in women and men. An acute coronary syndrome (ACS) with angiographically reported " normal" coronary arteries is more often shown in women than in men, at younger ages.[14,15] Various mechanisms are involved for this stated as coronary microvascular dysfunction and possibly connected to endothelial reactivity, low endogenous estrogen levels, coagulation disorders, and abnormal inflammatory reactions among individuals its appearance of substantial variability can be seen.[16]

The present study aimed to estimate the incidence of CAD among premenopausal women undergoing coronary angiography, detect the prevalence of various risk factors for CAD, and compare clinical characteristics and hormonal levels among premenopausal women with and without CAD.

MATERIALS AND METHODS

Study population

A total of 99 consecutive premenopausal women undergoing coronary angiography at our institute from January 2014 to January 2017 were recruited and medical records were analyzed in this single-center cross-sectional study. Postmenopausal females were excluded according to criteria laid down in the 2013 guidelines of the Indian menopause society.[17] At the discretion of the operating cardiologist on the basis of the patient's clinical profile, lesion characteristics, and patient preference, the decision to perform percutaneous coronary interventions (PCI) was made.

According to institution protocol, all patients signed written informed consent was collected before the procedure. All information interrelated to the patient's clinical presentation, the procedure, and follow-up was retrieved from the hospital information system where all such data related to patients were maintained with yearly follow-up information. Incomplete records were completed further using telephonic communication with the patients. To ensure the premenopausal status of the women, the correct information regarding the menstrual cycle regularity and the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations were assessed. The Institutional Ethics Committee approval was taken for the study. Perimenopausal females categories were interpreted by knowing the levels of FSH = 15–30 IU/L and FSH > LH, were excluded from the premenopausal group. Furthermore, women taking oral contraceptive pills or undergoing oophorectomy for any reason were excluded from the study. Patients that underwent only hysterectomy without oophorectomy were, however, included in the study.

Procedure protocol

All patients were subjected to invasive coronary angiography through the transfemoral or preferably trans-radial route as per institution protocol and performed using low or iso-osmolar iodinated contrast medium. Cardioactive medications were prescribed in accordance with the patient's clinical need and guidelines recommendation.

Evaluation tools

Using medical records, the data of clinical profile, coronary angiography, and traditional risk factors (age, family history, blood pressure, lipid profile, and blood glucose) were recollected. An echocardiogram was done to evaluate baseline left ventricular ejection function. Venous blood samples were collected on day 6 of menstruation to assess the relative increase in plasma estradiol, insulin, and progesterone levels during the menstrual cycle. A minimum of 8 h of fasting was observed for plasma insulin assessment in all patients. Reproductive hormone levels were measured using commercially available electrochemiluminescence immunoassay (Rosche Diagnostics® Cobas, Indianapolis, IN, USA).

Definitions

Premenopausal status

The definition of premenopausal status stated restricted current usage of oral contraceptive therapy or hormone, age ≤45 years LH > FSH and FSH <15 IU/L, and absence of any history of bilateral oophorectomy. In the algorithm, present menstrual cycling was not thought of as a determining factor or variable, because less no of premenopausal women presented with a history of a prior hysterectomy.

Statistical analysis

The Statistical Software named IBM SPSS (IBM SPSS, Statistics version 20.0, USA) was used for statistical analysis. All the continuous variables were stated as mean ± standard deviation and percentages were used for all categorical variables. All the obtained $P < 0.05$ were considered to be significant. The distribution of data was assessed using descriptive analysis. To study the relationship of each independent risk factor to the outcome of developing CAD or not, univariate logistic regression generated crude odds ratio was used. Multivariable regression was conducted to adjust for confounding variables and determine the factors independently associated with CAD. To compare the risk factor profile between groups of patients with CAD or without CAD, the Chi-square test was used.

RESULTS

Demographic profile

Baseline clinical and demographic characteristic of the patients according to CAD status after coronary angiography shown in Table 1. Overall, 99 patients were enrolled in the present study. Sixty-six (66.7%) premenopausal women had CAD on coronary angiography. Between the two groups, the mean age of the patients overall was 42.06 ± 3.47 years which did not differ significantly. The mean gap between event and sample collection in ACS patients was 58 ± 7 days.

Table 1: Baseline clinical and demographic characteristic of the patients according to CAD status after coronary angiography.

Variable	Overall (*n*=99)	CAD (*n*=66)	Non-CAD (*n*=33)	*P*-value
Age (mean±SD), years	42.06±3.47	42.44±3.35	41.30±3.63	0.13
Diabetes, *n* (%)	39 (39.4)	35 (53.0)	4 (12.1)	<0.0001
Hypertension, *n* (%)	46 (46.5)	36 (54.5)	10 (30.3)	0.02
Tobacco intake, *n* (%)	10 (10.1)	10 (15.1)	0 (0)	0.03
Family h/o CAD, *n* (%)	10 (10.1)	9 (13.6)	1 (3.0)	0.09
Mean LVEF (%)	51.16±8.79	50.61±8.78	52.27±8.85	0.38
LV dysfunction, *n* (%)	25 (25.3)	19 (28.8)	6 (18.2)	0.25
Mild (LVEF ≤30%)	13 (13.1)	11 (16.7)	2 (6.0)	0.24
Moderate (LVEF 31–49%)	11 (11.1)	9 (13.6)	2 (6.0)	
Severe (LVEF ≥50%)	4 (4.0)	2 (3.0)	2 (6.0)	
Clinical presentation, *n* (%)				
STEMI	23 (23.2)	23 (34.8)	0 (0)	<0.0001
NSTEMI	3 (3.0)	3 (4.5)	0 (0)	
Unstable angina	5 (5.1)	5 (7.6)	0 (0)	
Stable CAD	32 (32.3)	32 (48.5)	0 (0)	
Atypical chest pain	36 (36.4)	3 (4.5)	33 (100)	
Angiographic CAD pattern, *n* (%)				
Normal coronaries	33 (33.3)	0 (0)	33 (100)	<0.0001
1-vessel CAD	35 (35.4)	35 (53.0)	0 (0)	
2-vessel CAD	18 (18.2)	18 (27.3)	0 (0)	
3-vessel CAD	13 (13.1)	13 (19.7)	0 (0)	
ECG finding, *n* (%)				
Normal	61 (61.6)	35 (53.0)	26 (78.8)	<0.001
ST-T changes	37 (37.4)	31 (47)	6 (18.2)	
AF	1 (1.0)	0 (0)	1 (3.0)	
Treatment advised, *n* (%)				
Medical follow up	78 (78.8)	45 (68.2)	33 (100)	<0.001
PCI	15 (15.2)	15 (22.7)	0 (0)	
CABG	6 (6.1)	6 (9.1)	0 (0)	
Total cholesterol, mg/dL	143.75±35.11	144.21±33.15	142.82±39.28	0.85
Triglycerides, mg/dL	129.75±54.24	143.29±60.54	102.67±20.76	<0.0001
HDL cholesterol, mg/dL	36.96±7.90	34.88±7.57	41.12±6.92	<0.0001
LDL cholesterol, mg/dL	84.44±27.02	82.76±27.09	87.82±26.98	0.38
VLDL cholesterol, mg/dL	25.53±10.66	28.15±11.29	20.27±6.83	<0.0001

SD: Standard deviation, CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, LV: Left ventricular, STEMI-ST: Elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, ECG: Electrocardiogram, AF: Atrial fibrillation, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass surgery, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

Eight (8.1%) patients underwent hysterectomy before their enrolment in the study. Most of these patients (n = 6) knew the dates of their last menstrual period. For the few who did not remember their exact dates, an assumed date (i.e., 6th day of the month) was taken to maintain some sort of uniformity. In the CAD group, patients as compared to the non-CAD group observed a significantly higher number of patients with diabetes and hypertension conditions. One-fourth of patients had proof of left ventricular dysfunction. In the majority of non-CAD group, patient's electrocardiogram (ECG) was normal in comparison with the CAD group (78.8% vs. 53.0%) while half of the patients in the CAD group had ST-T changes as compared to 18.2% of non-CAD group patients (P = 0.01). Overall, 78 (78.8%) patients were advised medical treatment (including two-thirds of patients having angiographic CAD), whereas 15 (15.2%) and 6 (6.1%) patients were advised PCI and coronary artery bypass graft, respectively.

Hormonal assessment [Table 2]

Serum progesterone (2.20 ± 2.20 vs. 3.27 ± 2.62 ng/mL; P = 0.03), testosterone (0.67 ± 0.19 vs. 0.80 ± 0.34 nmol/L; P = 0.01), and insulin levels (7.22 ± 3.21 vs. 15.10 ± 14.58 μIU/mL; P = 0.0001) were significantly lower in premenopausal females having angiographic CAD. Between the groups [Table 2], no significant difference in levels of serum FSH and LH levels was obtained. On the contrary, patients having CAD demonstrated higher serum estradiol levels as compared to non-CAD patients (145.45 ± 114.34 pg/mL vs. 67.84 ± 19.52 pg/mL; P < 0.0001).

Overall, 39 patients had diabetes out of which 35 had some form of CAD. 47% (n = 31) of CAD patients were non-diabetic. Only four patients were on insulin therapy. Irrespective of diabetic status, insulin levels were observed to be lower in CAD patients [Table 3]. Therefore, insulin levels were related to CAD independent of diabetic status in our study. Despite the trend being non-significant, in diabetics, patients noted lower fasting insulin levels when compared to non-diabetic premenopausal women (8.05 ± 3.75 vs. 11.02 ± 11.71 μIU/mL; P = 0.071). Perhaps, this trend could have been found to be significant if the sample size was more.

Predictors of angiographic CAD in premenopausal women

Univariate analysis showed that diabetes mellitus, hypertension, tobacco intake, triglycerides, HDL cholesterol, very low-density lipoprotein cholesterol, estradiol, progesterone, testosterone, and insulin were significantly predictive of CAD. Multivariate linear regression analysis was used, after adjustment for confounding risk factors, diabetes mellitus (adjusted odds ratio [AOR] 16.46; P = 0.006 [95% confidence interval, CI: 2.21–122.41]), triglycerides (AOR 1.05; P = 0.002 [95% CI: 1.02–1.10]), progesterone (AOR 0.68; P = 0.015 [95% CI: 0.50–0.93]), and insulin (AOR 0.51; P < 0.0001 [95% CI: 0.38–0.70]) were found to independently predict the development of CAD [Table 4].

DISCUSSION

Premenopausal women despite having relatively low-risk factors, the prevalence of CAD is substantial as shown in various studies. In our study, 66.7% of the study population had angiographic CAD, while the WISE study[5] had angiographic CAD in 20% of 123 premenopausal women included in the trial. The high incidence of angiographic CAD in our population can be attributed to the high pre-test probability of the sample population. Patients with angiographic CAD showed a trend toward high blood pressure as compared to those who did not have CAD in accordance with WISE results[5] which showed SBP as one of the risk factors for the development of CAD in premenopausal women (P = 0.002) independent of age and menopausal status. Tobacco intake has been one of the risk factors for developing CAD and it has been shown in various earlier studies. Furthermore, a significant number (n = 23; 23.3%) of patients presenting with ST-elevation myocardial infarction in our study represented a bias in favor of tobacco-related acute thrombotic events.

Three-fifth of patients had normal ECG at presentation of which more than 50% had angiographic evidence of CAD. Only 37.4% of patients had ECG changes typical of ischemia in the form of ST-T changes. According to published report by Mieres *et al.*[18] the lower sensitivity and specificity of non invasive testing in women is due to factors such as non

Table 2: Hormonal analysis.

Variable	Overall (n=99)	CAD (n=66)	Non-CAD (n=33)	P-value
Progesterone (ng/mL)	2.56±2.39	2.20±2.20	3.27±2.62	0.03
FSH (μIU/mL)	8.84±4.99	9.09±5.26	8.34±4.40	0.48
LH (IU/mL)	10.73±5.66	10.63±5.27	10.91±6.44	0.82
Testosterone (nmol/L)	0.72±0.26	0.67±0.19	0.80±0.34	0.01
Insulin (μIU/mL)	9.85±9.50	7.22±3.21	15.10±14.58	<0.0001
Estradiol (pg/mL)	119.58±30.74	145.45±14.34	67.84±19.52	<0.0001

FSH: Follicular-stimulating hormone, LH: Luteinizing hormone, CAD: Coronary artery disease

Table 3: Distribution of fasting serum Insulin levels (in μIU/mL) in premenopausal women according to diabetic and CAD status.

CAD	Diabetes mellitus		*P*-value
	Yes (*n*=39)	No (*n*=60)	
Yes (*n*=66)	7.22±3.11 (35)	6.90±2.90 (31)	0.823
No (*n*=33)	12.76±2.60 (4)	15.42±15.53 (29)	0.852
P-value	0.004	<0.0001	

CAD: Coronary artery disease

Table 4: Multivariate predictors of angiographic CAD in premenopausal women.

	OR	95% CI	*P*-value
Diabetes	16.46	2.21–122.41	0.006
Triglycerides	1.05	1.02–1.10	0.002
Progesterone	0.68	0.50–0.93	0.015
Insulin	0.51	0.38–0.70	<0.0001

CAD: Coronary artery disease, CI: Confidence interval, OR: Odd's ratio

specific ECG changes at rest, lower exercise capacity, and a smaller vessel size. About 36.4% (n = 36) patients had atypical chest pain at presentation, the majority (n = 33) of which had no evidence of atherosclerosis involving epicardial coronary arteries explained by abnormal cardiac nociception that point to persistent chest pain due to increased coronary pain perception in women.[19] However, it has been seen that women who are presented with non-cardiac chest pain show a twofold increased risk to develop a CHD event in the upcoming 5–7 years and require a 4 times higher risk for re-hospitalizations and recurrent angiograms in the succeeding 180 days.[20,21]

Previous data have shown SHBG to be positively associated with HDL[22] and physical fitness[23] and negatively associated with obesity[22,24,25] upward fat distribution,[26] triglycerides,[27] insulin resistance,[26,28,29] and diabetes.[24,30] The positive correlation between HDL and SHBG is thought to be due to the influence of SHBG on the metabolism and/or production of HDL,[11] although the precise mechanism is unknown. Conventionally, endogenous estrogens mainly estradiol (E2) have been known to confer CV protection in women. Estradiol levels were found to be more than 2-fold high in premenopausal women with angiographic CAD, contrary to the concept of hypothalamic hypoestrogenemia established by the WISE study.[5] However, in our study, gonadotropin-releasing hormone levels have not been estimated. Furthermore, excess endogenous estrogen formation in CAD patients could be extragonadal in origin. Gonadotropin and estrogen receptor insensitivity or resistance in premenopausal women can also explain CAD in the presence of functional estrogen deficiency despite having elevated estrogen levels. Protein-bound hormones and inactive forms of estradiol may result in lower biological activity despite high serum levels. This calls for further research in the field of reproductive hormones modulating various risk factors contributing to the development of CAD in premenopausal women.

Historically, hyperinsulinemia is considered a surrogate marker for insulin resistance, predicts incident CHD, and was reported in studies performed on a larger population. Vafaeimanesh *et al*. assessed insulin resistance and its correlation with CAD in 120 non-diabetic (including 56 females) patients[31] and not found any significant difference in insulin levels and homeostatic model assessment-insulin resistance (HOMA-IR) with respect to the presence or absence of CAD, especially in women. However, HOMA-IR correlated with the severity of CAD and the prevalence of metabolic syndrome. Similarly, Vonbank *et al*. found that HOMA-IR is not associated with angiographically significant CAD.[32] Although the inability to assess insulin resistance is one of the important limitations of the study, serum insulin levels if collected with a predetermined protocol of 8-h fasting may provide some uniformity as a surrogate marker for comparison. Furthermore, it was noted that there was an inverse relation of insulin levels to age. In the above-described studies, the mean age of the females included was >50 years, but our study included only premenopausal females with a mean age of 42.06 ± 3.47 years which can be a possible explanation for relatively higher insulin levels in our study population.

In women having angiographic CAD, serum progesterone and insulin levels were also observed to be significantly lower. Data in premenopausal CAD patients assessing insulin levels are scarce. However, we do have a corroborative hypothesis explaining the possible association of insulin levels with CAD. Insulin has a direct inhibitory effect on SHBG.[33,34] Low SHBG is known to be associated with obesity, hypertriglyceridemia, low HDL, and insulin resistance. Hence, low insulin levels may lead to upregulation of SHBG which, in turn, affects the atherosclerotic disease modifiers for the better. Progesterone may play important role for inhibiting the migration of macrophages and may lead to weak intracellular lipid turnover, thus having athero-protective effects.[35] In addition, progesterone deficiency may be responsible for promoting the proatherogenic effect of aldosterone.[36] Progesterone has been shown to have a small intrinsic androgenetic activity at extra-gonadal sites. Few clinical studies showed lower progesterone levels to be associated with smoking, sedentary lifestyle, and obesity in post-MI premenopausal women.[37,38] Anecdotal evidence also suggests that bioidentical micronized progesterone administration with or without estradiol has a favorable effect on serum HDL, flow-mediated dilation, triglycerides,

and exercise tolerance as reported in postmenopausal women presented with CAD or previous history of MI.[39-42] High androgen levels were associated with alterations in glucose, metabolism adverse lipid profile, high blood pressure, and higher subclinical and clinical atherosclerosis leading to higher CV events;[43-45] yet, testosterone levels were not found to be significantly different in patients with or without CAD on multivariate analysis in our study. More research is essential to conclusively deduce the pathophysiological and clinical relevance of the finding of lower insulin and progesterone levels in premenopausal females with CAD.

Limitation

There are a few limitations. This was a single-center experience with an observational and non-randomized study design. The rural versus urban populations have not been assessed in our study. Dyslipidemia with levels of lipoproteins A and homocysteine high-sensitivity C-reactive protein was not assessed. The present study demonstrates an independent predictive value of sex hormones in premenopausal females yet a causal relationship to the development of CAD cannot be deduced. Investigation of the sources and specific molecular forms of sex hormones is warranted. Furthermore, the applicability of these results to the male population is not known. An imperative limitation is a failure to take into account the total effect of the combined adrenal androgens, with dehydroepiandrosterone sulfate, androstenediol, and androstenedione. The above described hormones and their peripheral conversion products are likely to contribute for the total circulating bioactive androgen level and act with testosterone to further reduce SHBG levels.

CONCLUSION

A significant proportion (approximately two-thirds) of premenopausal females in the study group were detected to have underlying CAD. Disturbance in hormonal homeostasis in the form of decreased insulin and progesterone levels may manifest as hypertriglyceridemia and diabetes mellitus that may be responsible for accelerating atherosclerosis in premenopausal females. Incorporation of these metabolic variables into the protocols of large, prospective outcome-driven trials, with randomization to differing strategies will help establish their value as a marker for predicting the development of CAD in this subset of patients and also to guide relevant therapy.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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What is already known?

There is a small but rapidly growing population of premenopausal women having CAD. Initial observational studies (e.g., WISE study) have shown that endogenous estrogen deficiency predisposes to increased coronary artery risk in premenopausal women cohort. However, SWAN trial suggested the role of sex hormone-binding globulin (SHBG) and androgens, linking them to dyslipidemia, dysglycemia, obesity, and metabolic syndrome.

What this study adds?

This study adds to the existing evidence that apart from estrogen deficiency, newer hormonal imbalances in the form of low progesterone and hypoinsulinemia may contribute to hypertriglyceridemia and diabetes in premenopausal women, thereby predisposing them to coronary atherosclerosis. These hormonal markers can therefore be used to predict angiographic CAD in premenopausal females. This study is one of the few to present Indian hormonal data regarding CAD in premenopausal women.