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Hysterectomy Enhances the Risk of Coronary Artery Disease in Type 2 Diabetic Women in Premenopausal Age Group

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Abstract

Aim: *In this study we aim 1) to assess the associated risk for Coronary Artery Disease (CAD) in premenopausal and postmenopausal stage in women and 2) to determine the impact of hysterectomy in women with type 2 diabetes mellitus in premenoupausal age, on the risk of CAD.*

Methods: *A total of 181 type 2 diabetic women who underwent exercise treadmill ECG testing in the hospital during a 30 months period was studied. Based on an arbitrary cut off age of 48 yrs subjects were assigned in group 1: age < 48 yrs (premenopausal) and group 2: age ≥ 48 years (postmenopausal). Based on exercise treadmill ECG results, they were subgrouped as without CAD (treadmill ECG test negative) and with CAD (treadmill ECG test positive).*

Results: *Age, duration of diabetes, hypertension and CAD were significantly more in postmenopausal group ($p<0.05$). Age, HDL-cholesterol and hysterectomy were significantly ($p< 0.05$) associated with premenopausal CAD. In postmenopausal CAD subgroup age, duration of diabetes, hypertension, HDL-cholesterol, sedentary physical activity and hysterectomy were significantly higher ($p<0.05$). In the multivariate analysis, hysterectomy was strongly associated (OR = 7.73, p = 0.016) with premenopausal CAD. Conclusion: The study projects hysterectomy as a high risk factor for the CAD in premenopausal type 2 diabetics.*

Keywords: *Type 2 diabetes, age, hysterectomy, coronary artery disease.*

1. INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide, with the heaviest toll in developing countries. Both type 1 and type 2 diabetes increase cardiovascular risk 2 – 4 fold compared with the general population – a risk level that may compare with that of non-diabetic people who have already suffered a myocardial infarct [1]. Many think of CAD as primarily a problem of men, perhaps

because men have more than twice the total incidence of cardiovascular morbidity and mortality than women between the ages of 35 – 84 [2]. The simplest explanation for the sex difference in CAD is a "cardio-protective" effect of estrogen, due to improvement of the lipid profile, a direct vasodilatory effect, and perhaps other factors [2]. However, many studies have reported that the premenopausal protection against coronary heart disease seen in healthy women is lost in those with diabetes [1]. Women with diabetes mellitus have twice the risk of myocardial infarction as non-diabetic women and the same risk of a myocardial infarction as a non-diabetic male of the same age [3]. In fact, the increased risk associated with diabetes appears to be synergistic with gender. In one study, cardiovascular mortality rates were 3 – 7 folder higher in diabetic women than non-diabetic women, as compared to 2 – 4 folder higher in diabetic men than in non-diabetic men [4]. In view of the gender differences in the risk for CAD and also the variations that occur in postmenopausal stage in women, the present study was done with the aim 1) to assess the associated risk for CAD in premenopausal and postmenopausal stage in women and 2) to determine the impact of hysterectomy in women with type 2 diabetes mellitus in premenopausal age, on the risk of CAD.

2. MATERIALS AND METHODS:

Selection of subjects: Ethical approval of the study protocol was obtained from the institution's ethics committee. The study subjects gave their informed consent for the study. Consecutive female patients of type 2 diabetes (n = 181) who had undergone exercise treadmill ECG testing in M.V. Hospital for Diabetes and Diabetes Research Centre, Chennai during a period of 30 months (from 1.02.03 to 31.07.05) were studied. The selection criteria included type 2 diabetes by the WHO criteria [5] with availability of all relevant clinical and laboratory data at the time of study. For non-invasive detection of CAD the exercise treadmill ECG test was used [6]. According to ACC/AHA guidelines it is considered appropriate for the diagnosis of obstructive CAD in adult patients (including those with complete RBBB or < 1mm of resting ECG depression) with an intermediate pretest probability of CAD based on gender, age and symptoms [7]. Its sensitivity is 68% and specificity is 77% in the diagnosis of CAD [8]. We used modified Bruce's protocol for exercise treadmill ECG test. Age of 48 year was taken arbitrarily as the age of menopause and based on that the recruited subjects were assigned into two categories and subgroups were based on exercise, treadmill ECG results:

Group 1: age below 48 year (premenopausal group)

Subgroup A: premenopausal without CAD (exercise treadmill ECG test result negative)

Subgroup B: premenopausal with CAD (exercise treadmill ECG test result positive)

Group 2: age 48 year and above (post menopausal group).

Subgroup C: postmenopausal without CAD (exercise treadmill ECG test result negative) and

Subgroup D: postmenopausal with CAD (exercise treadmill ECG test result positive)

The variables were recorded in each subgroup at the time of the treadmill ECG testing. Body mass index (BMI kg/m^2), history of angina, duration of diabetes, glycosylated haemoglobin (HbA1c), treatment of diabetes and family history of ischaemic heart disease (IHD) were recorded. History of hypertension (HTN) and treatment of HTN were noted. Blood pressure (BP) was measured at the time of the study as mean of three sphygmomanometer readings taken after 5 minutes rest at each time, in the sitting position. The goal for blood pressure was taken as BP < 130 / 80 mmHg as per recent JNC VII report [9] and categorised as controlled or uncontrolled hypertension in each subgroup. History of treatment with aspirin and history of hysterectomy were recorded.

Resting ECG was recorded and the criteria for abnormal ECG were T wave inversion, T wave flattening, ST depression and pathological Q wave. Echocardiography were done and criteria documented as abnormal reading was regional wall motion abnormality (RWMA), LV dysfunction and LV hypertrophy. Anti-lipid treatment was also documented. Complications included diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and peripheral vascular disease. Data regarding physical activity, as per ADA recommendation [10] and diet habits were also recorded (vegetarian or non-vegetarian).

Biochemical Tests: Blood samples were collected to determine the biochemical parameters including glycosylated haemoglobin (HbA1c), total cholesterol and triglycerides. HbA1c was quantitatively determined by the turbidimetric inhibition immunoassay using hemolyzed whole blood. Fasting serum sample was used to estimate total cholesterol and its fractions like high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and triglycerides (TG). All the above biochemical tests were done using the reagents from Roche Diagnostics, Mannheim, Germany and were used on the Hitachi auto analyzer 902 system. Albuminuria (by immunoturbidimetry) was estimated in spot collection in the morning sample or in 24-hour urine collection.

Statistical Analysis: Data with normal distribution were expressed as mean ± S.D. Comparisons of the group means were performed by unpaired student's 't' test. Intergroup comparisons were made by one-way ANOVA. Multiple range tests by Duncan procedure was employed to identify the significant groups at 5% level. Chi-square test was done to compare the proportions between the groups. Multiple logistic regression analysis with stepwise addition of independent variables was done to find out the parameters associated with premenopausal CAD. P values less than 0.05 were considered as statistically significant. All the tests were performed using SPSS / PC + package.

3. RESULTS

Table 1 shows anthropometric, clinical and biochemical characteristics of premenopausal and postmenopausal subjects. As expected group 2 study subjects were older (mean age: 54.4 ± 4.7 years, $p < 0.0001$), having higher duration of diabetes ($p < 0.001$), more CAD ($\chi^2=11.2$, $p< 0.0001$) and more hypertension ($\chi^2 = 6.6$, $p < 0.01$) comparing with group 1.

TABLE 1: Anthropometric, Clinical And Biochemical Characteristics Of Premenopausal And Postmenopausal Subjects

	Group 1 Premenopausal	**Group 2 Post menopausal**
n	73	108
Age (yrs)	42 ± 4.6	54.4 ± 4.7 *
BMI (kg/m^2)	28 ± 4.6	27.9 ± 4.1
Duration of diabetes (yrs)	6.9 ± 5.3	9.8 ± 5.97 *
HbA1c (%)	8.6 ± 2	8.5 ± 2.1
TG (mg/dl)	221 ± 173	193± 140
HDL-C (mg/dl)	48 ± 10.0	49 ± 10
LDL-C (mg/dl)	112 ± 40	119 ± 39
Values are mean ± S.D.		
CAD (n (%))	20 (27.4)	58 (53.7) *
Family history of IHD (n (%))	27 (37)	27 (25)
History of hypertension (n (%))	31 (42.5)	68 (63) *
Uncontrolled hypertension (n (%))	24 (32.9)	51 (47.2)
Hysterectomy (n (%))	12 (16.4)	26 (24 .1)
Albuminuria (n (%))	21 (28.8)	32 (29.6)
Sedentary physical activity (n (%))	42 (57.5)	76 (70.4)
Diet – Vegetarian (n (%))	17 (23.3)	27 (25)
Diet – Non – Vegetarian (n (%))	56 (76.7)	81 (75)

VALUES are n (%),IHD = Ischaemic heart disease, CAD = Coronary artery disease. * $p < 0.05$

Table 2 shows anthropometric, clinical and biochemical characteristics of premenopausal and postmenopausal subjects in different subgroups. Age was significantly higher in sub group B, C and D compared to sub group A ($p<0.0001$). Mean BMI was high in all the sub groups and with no significant intergroup differences. Duration of diabetes was significantly higher in C and D subgroup compared with subgroup A ($p< 0.001$). Glycosylated haemoglobin, triglyceride

and LDL cholesterol were not statistically significant among the four sub groups. HDL Cholesterol was significantly low in both subgroup B and D compared to subgroup A ($p < 0.03$) and subgroup C ($p<0.03$). There was no significant difference in the family history of IHD, albuminuria and diet among the four groups of patients. Statistical significance was noted between subgroup D compared to subgroup A in history of hypertension ($\chi^2 = 5.07$, $p < 0.02$), uncontrolled hypertension ($\chi^2 = 10.4$, $p < 0.001$) and sedentary physical activity ($\chi^2 = 9$, $p < 0.04$). Hysterectomy was more common in subgroup B ($\chi^2 = 8.9$, $p < 0.003$) and also significant in subgroup C ($\chi^2 = 4.13$, $p < 0.04$) and subgroup D ($\chi^2 = 4.46$, $p < 0.03$) compared to subgroup A.

TABLE 2: Anthropometric, Clinical And Biochemical Characteristics Of Premenopausal And Postmenopausal Subjects With Or Without Cad.

	Group 1 Premenopausal (n = 73)		**Group 2 Post menopausal (n = 108)**	
	Subgroup A Without CAD	**Subgroup B With CAD**	**Subgroup C Without CAD**	**Subgroup D With CAD**
N	53	20	50	58
Age (yrs)	41.3 ± 4.7	44.2 ± 2.9*	54.5 ± 4.6 *,#	54.4 ± 4.8 *,#
BMI (kg/m^2)	27.7 ± 4.9	27.8 ± 3.1	28.3 ± 4.6	27.5 ± 3.7
Duration of diabetes (yrs)	6.1 ± 4.3	8.9 ± 6.9	8.8 ± 5.7 *	10.7 ± 6 *
HbA1c (%)	8.5 ± 1.9	8.9 ± 2.3	8.5 ± 2.2	8.5 ± 1.9
TG (mg/dl)	226 ± 198	208 ± 86	193 ±177	194 ± 100
HDL-C (mg/dl)	49 ± 11	43 ± 6 *,@	50 ± 9	46 ± 11 @
LDL-C (mg/dl)	107 ± 39	123 ± 41	115 ± 39	122 ± 40
Values are mean ± S.D.				
Family history of IHD (n (%))	18 (34)	9 (45)	8 (16)	19 (32.8)
History of hypertension (n (%))	20 (37.7)	11 (55)	27 (54)	41 (70.7) *
Uncontrolled hypertension (n (%))	14 (26.4)	10 (50)	17 (34)	34 (58.6) *
Hysterectomy (n (%))	4 (7.5)	8 (40) *	12 (24) *	14 (24.1) *
Albuminuria (n (%))	12 (22.6)	9 (45)	10 (20)	22 (37.9)
Sedentary physical activity (n (%))	29 (54.7)	13 (65)	28 (56)	48 (82.7) *
Diet – Vegetarian (n (%))	12 (22.6)	5 (25)	11 (22)	16 (27.6)
Diet – Non – Vegetarian (n (%))	41 (77.4)	15 (75)	39 (78)	42 (72.4)

VALUES are n (%),IHD = Ischaemic heart disease. * p (< 0.05) vs sub group A; # p (< 0.05) vs sub group B; @ p (< 0.05) vs sub group C

Table 3 shows the clinical profile of the study subjects. As expected angina was more common in subjects with CAD in both groups. Neuropathy and retinopathy were more common than peripheral vascular disease.

TABLE 3: Clinical Profile Of The Study Subjects.

	Group 1 (Premenopausal)			**Group 2 (Post menopausal)**		
	Total	**Sub Group A Without CAD**	**Sub Group B With CAD**	**Total**	**Sub Group C Without CAD**	**Sub Group D With CAD**
n	73	53	20	108	50	58
On oral hypoglycaemic agents (n (%))	56 (76)	44 (83)	12 (60)	72 (67)	37 (74)	35 (60.4)
On insulin + oral hypoglycaemic agents (n (%))	17 (24)	11 (20.8)	6 (30)	36 (33)	13 (26)	23 (39.7)
On aspirin therapy (n (%))	14 (19)	11 (20.8)	3 (15)	23 (21)	8 (16)	15 (25.9)
On lipid-lowering agents (n (%))	13 (18)	9 (17)	4 (20)	22 (20)	10 (20)	12 (20.7)
History of angina (n (%))	41 (56)	25 (47.2)	16 (80)	66 (61)	24 (48)	42 (72.4)
Abnormal ECG (n (%))	39 (53)	26 (49)	13 (65)	52 (48)	25 (50)	27 (46.6)
Abnormal echocardiography (n (%))	5 (7)	3 (5.7)	2 (10)	24 (22)	11 (22)	13 (22.4)
Diabetic neuropathy (n (%))	10 (14)	4 (7.5)	6 (30)	24 (22)	8 (16)	16 (27.6)
Diabetic retinopathy (n (%))	8 (11)	5 (9.4)	3 (15)	30 (28)	10 (20)	20 (34.5)
Peripheral vascular disease (n (%))		------	------	1 (0.9)	------	1 (1.7)

Table 4 shows the significant associations of risk factors with CAD in the premenopausal and postmenopausal groups evaluated by multiple logistic regression analysis. Age (OR = 1.24, p = 0.044), hysterectomy (OR = 7.73, P = 0.016) and low HDL cholesterol (OR = 0.914, p = 0.046) were significantly associated with premenopausal CAD. The strongest association was between hysterectomy and premenopausal CAD. In the postmenopausal group hysterectomy was not an associated risk factor for CAD.

TABLE 4: Results of multiple logistic regression analyses:

A - Dependent variable - Premenopausal group CAD versus non – CAD.

	β	SEβ	P value	OR
Age (years)	0.211	0.105	0.044	1.24
Hysterectomy	2.045	0.847	0.016	7.73
HDL –C (mg/dl)	- 0.09	0.045	0.046	0.914

B - Dependent variable - Postmenopausal group CAD versus non – CAD.

	β	SEβ	P value	OR
Family history of IHD	1.22	0.56	0.028	3.38
Uncontrolled hypertension	- 1.16	0.46	0.011	0.31
Triglyceride (mg/dl)	0.008	0.004	0.034	1.008
Sedentary physical activity	- 1.27	0.499	0.011	0.281

Independent variables: age, body mass index, duration of diabetes, glycosylated haemoglobin, family history of IHD, history of hypertension, uncontrolled hypertension, albuminuria, hysterectomy, triglyceride, HDL cholesterol, LDL cholesterol, physical activity, diet.

Significant variables are shown.

OR = odds ratio.

4. DISCUSSION

In this study we have investigated the profile of premenopausal and postmenopausal subjects with and without CAD, classified on the basis of exercise treadmill ECG testing. The risk variables specifically associated with CAD in premenopausal subjects were looked for. The study population was from different parts of urban India and the patients belonged to the upper – middle and high socio-economic class.

In women establishing the diagnosis of CAD remains problematic and this is, in part, due to the relatively high prevalence of chest pain in women in the absence of significant epicardial coronary artery stenosis [11]. Over 50% of women may have angina pectoralis as their first symptoms [12]. One of the initial studies to recognize the

diagnostic value of angina in women was the coronary artery surgery study (CASS) and they found 72% of the women with definite angina and 36% of the women with probable angina were having significant coronary disease, defined as at least 70% coronary artery stenosis [13]. In a sub-analysis we found that 59% of women presented with angina and out of them 54% had CAD defined by exercise treadmill ECG testing. Univariate analysis showed that age, duration of diabetes, history of hypertension, uncontrolled blood pressure, HDL cholesterol, hysterectomy and sedentary physical activity were significantly related to postmenopausal CAD. Whereas in premenopausal CAD age, HDL cholesterol and hysterectomy were significant. Age was strongly associated with premenopausal and postmenopausal CAD. Krolweski AS et al., [14] showed that in patients with type 1 diabetes the risk of CAD increases rapidly after the age of 40. We found that history of hypertension and uncontrolled hypertensions were significant in postmenopausal CAD. Women have a higher incidence of hypertensive heart disease and common causes of hypertension, such as renovascular hypertension due to fibromuscular dysplasia, are more common in women than in men [15, 16].

The Framingham study was the first to demonstrate the association of low HDL levels with CAD [17]. Studies have shown that for every 1 mg decrease in HDL cholesterol the risk for heart disease increased by 2% in men and 3% in women [18, 19]. In fact, decreased HDL cholesterol levels are a stronger predictor of risk in women than in men [20, 21]; elevated LDL cholesterol levels, a strong predictor of atherosclerotic heart disease in men, do not contribute as strong a risk factor for CAD as low HDL cholesterol levels in women who do not have established clinical coronary disease [22, 23] and elevated triglyceride levels also appear to be an independent predictor of coronary disease in older women [22]. In our study we found that low HDL cholesterol levels were significantly associated with premenopausal and postmenopausal CAD. LDL cholesterol was not significant in CAD in our study. Triglycerides were significantly associated with postmenopausal CAD.

Univariate analysis showed that hysterectomy was significantly associated with CAD of both groups. In the multivariate analysis hysterectomy was found to be strongly and independently associated only with premenopausal CAD, while conventional risk factors such as family history of IHD, uncontrolled hypertension, increased triglyceride and lack of physical activity were significantly associated with occurrence of postmenopausal CAD. There is not many report regarding role of hysterectomy as an associated risk factor for CAD in women. The large scale epidemiological studies have shown that restoration of the premenopausal hormones with hormone replacement therapy (HRT) is associated with 30% to 50% reduction in death from cardiovascular disease [24, 25, 26]. However based on the results of the Heart and Estrogen / Progestin Replacement Study (HERS) and Women's Health Initiative (WHI) study, HRT is

not recommended for any women with or without diabetes, as a therapeutic strategy for primary or secondary prevention of CAD [27, 28].

Several trials form the basis for the current American Heart Association / American College of Cardiology (AHA / ACCC) recommendation that HRT does not play a role in the primary prevention of CAD; however, for women who presently take estrogen compounds, there is no benefit to discontinue this therapy [29]. Confounding clinical decisions regarding the initiation of HRT is a recently published study from Heart and Estrogen / Progestin Replacement study (HERS) in which HRT reduced the incidence of diabetes by 35% [30].

However, our observations support the risk enhancement by hysterectomy, but those are insufficient to recommend the use of hormones for prevention of either diabetes or CAD. Results from Women's Health Initiative (WHI) study regarding the use of estrogen replacement therapy (ERT) alone in hysterectomized women have not yet been published, and there are no prospective data to guide health care providers in advising in favour of or against this therapy [31]. The mechanisms by which diabetes abolishes the cardiovascular protective effects of female sex hormones are not well understood. However, one recently described mechanisms involves the interaction between hyperglycaemia and estradiol in regulation of endothelial cell 'NO' (nitric oxide) production; where hyperglycaemia reduces the estradiol mediated production of 'NO' from vascular endothelial cells, which may contribute to the accelerated atherosclerosis in diabetic women [32, 33].

The study projects hysterectomy as a high risk factor for the CAD in premenopausal type 2 diabetics. The study underscores the need to assess hysterectomy in case of premenopausal type 2 diabetic women in view of the risk for CAD. More information from prospective long-term clinical trials targeted to answer the questions regarding the loss of premenopausal protection of CAD in diabetes and the optimal treatment strategies for both premenopausal diabetic women and CAD will help to guide therapy in the future.

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