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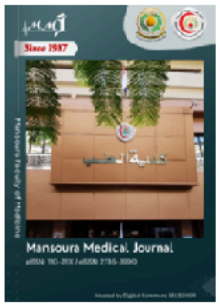

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SEX HORMONES AND OXIDANT- ANTIOXIDANT STATUS IN POST-MENOPAUSAL WOMEN WITH CORONARY ARTERY DISEASE

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ABSTRACT

Background : The strikingly lower prevalence of acute coronary syndromes in pre-menopausal women than in men of similar age, then the progressive narrowing of that difference with age after menopause, suggests an important role for sex hormones and probably oxidative stress in the development of coronary artery disease.

Objective : The aim of this study is to evaluate the sex hormones and oxidant stress (malondialdehyde, which is a metabolite of lipid peroxidation) and anti-oxidants (vitamin C and E) status in postmenopausal women with stable coronary artery disease and in those with acute coronary syndromes.

Subjects & Methods : This study was conducted on 40 non-hormone user postmenopausal women with coronary artery disease. They were divided into 3 groups: the 1st group (17 patients) who had an acute myocardial infarction, the 2nd group (10 patients) had unstable angina and the 3rd one (13 patients) had stable angina. This is in addition to 20 apparently healthy postmenopausal women of similar age. All cases and control subjects were subjected to thorough history taking, full clinical examination, routine laboratory investigations, resting echocardiography and special la-

boratory investigations including detection of serum levels of; total & free testosterone, total estradiol, morning & nocturnal serum cortisol, malondialdehyde and plasma levels of α-tocopherol and vitamin-C .

Results : We found a higher serum level of total and free testosterone in cases than control subjects (P-value 0.016 & 0.031 respectively) and the serum free testosterone was significantly higher in the group of acute myocardial infarction than the group of stable angina (P-value 0.008). The serum level of total estradiol was significantly lower in cases than in control group (P value 0.0001).

Serum malondialdehyde was significantly higher in cases than control subjects (P<0.0001), and it was significantly higher in cases of acute myocardial infarction in comparison to stable angina cases (P-value 0.005). Vitamin E (α-tocopherol) and vitamin C were significantly lower in cases than control group (P<0.0001 & 0.048 respectively).

Conclusion : The serum levels of free testosterone as well as malondialdehyde were higher in postmenopausal women with coronary artery disease. However, serum level of estradiol, vitamin E and C were lower in them in comparison to control subjects.

INTRODUCTION

The strikingly lower prevalence of AMI (acute myocardial infarction) in the premenopausal women than in men of similar age [1], then the progressive narrowing of that difference with age after menopause [2], and an inability to explain the difference by known risk factors for AMI other than gender [3] suggest an important role for sex hormones and probably oxidative stress in the development of CAD (coronary artery disease).

While numerous cross-sectional and prospective studies on plasma sex hormone levels in relation to CAD have been performed in men, there are conflicting results as regard the relation of sex hormones to CAD in postmenopausal women. Some studies had found that free testosterone and FAI (free androgen index; which is the molar ratio of total testosterone/ SHBG and is said to be highly correlated with free testosterone) had a

positive correlation with CAD like Cathryn et al (2003)[4] and Gerald et al (1997)[5], while others had found that a lower testosterone level in postmenopausal women was positively correlated with CAD like Agnieszka et al (2003)[6].

Oxidative stress has been implicated in the pathogenesis of CVD (cardiovascular disease) [7,8]. The oxidative modification of LDL-C (low density lipoprotein-cholesterol) is believed to play a key role in the progression of atherosclerosis [9-11]. One of the oxidized forms, malondialdehyde (MDA) has been isolated from the sera of patients with CAD [12]. It has been suggested that increased oxidative stress, related to an unbalanced pro-oxidant/ antioxidant equilibrium, is a potential inducer of cardiovascular risk [13]. The atheroprotective effect of estrogen might also be partly due to its antioxidant action [14], resulting in a decrease of LDL-C oxidation [15].

During aging, a decrease of antioxidant enzymes [16] as well as a lower antioxidant nutrients has been reported [17,18]. Despite the key role of antioxidant micronutrients in preventing accelerated aging, the data related to relationship between oxidative stress and antioxidant status in postmenopausal women are not extensive.

AIM OF THE WORK

The aim of this work is to study the level of sex hormones, malondiialdehyde (MDA) and antioxidant vitamins E (α-tocopherol) and vitamin C (ascorbic acid) in postmenopausal women with CAD.

SUBJECTS AND METHODS

This study was conducted on 40 postmenopausal women with CAD, taken from the outpatient, inpatient & coronary care unit, cardiology departement, Specialized Medical Hospital, Mansoura University. They were divided 3 groups:

Group 1 : 17 patients had acute myocardial infarction (AMI)

Group 2 : 10 patients had unstable angina (UA)

Group 3 : 13 patients had stable angina (SA)

The patients diagnosed as having SA by history of classic chest pain on effort, characteristic ECG changes,

segmental wall motion abnormalities (SWMA) detected at echocardiography and/or had a previous positive diagnostic coronary angiography for CAD [19]. The patients who were diagnosed as having AMI if they had 2 of the following: [1] chest pain > 30 minutes. [2] ≥ 2 fold increase of serum CK (creatine phosphokinase) with elevation of MB isoform ≥ 10% (3) persistent ischemic ECG changes: evolution of pathologic Q-waves (≥ 00.04 second), or ≥ 0.1 mV, ST-segment deviation in at least 2 contiguous leads (ST-elevation MI), or ≥ 0.1 mV ST depression or definite T-wave inversion (non-ST elevation MI) or new left bundle branch block (LBBB) (20). The patients diagnosed as having UA, i f they had one of the following :

- Cresendo angina (more severe or frequent) superimposed on chronic stable angina.
- Angina at rest or with minimal activity.
- New onset angina (within 1 month) that is brought on by minimal exertion [21].

This is in addition to 20 apparently healthy postmenopausal women as a control group.

Exclusion criteria :

We exclude the following patients:

1- Patients with major organ failure i.e. heart, respiratory, liver or renal failure.
2- Patients with other endocrine disorders rather than diabetes mellitus (DM).
3- Cancer patients.
4- Patients with active infection or auto-immune diseases.
5- Patients who diagnosed as having major psychiatric diseases such as depression.
6- Those who had undergone hysterectomy &/or ovariectomy.
7- Patients taking hormone replacement therapy, hypolipidaemic drugs or antioxidant vitamin supplements.
8- Patients taking digitalis, which has been reported to affect the estradiol and testosterone levels [22].

All cases and control subjects were undergone the following:

1) Thorough history taking with special stress on chest pain suggestive of CAD, past history of cardiac

events and interventions done for the patient.

2) Clinical examination including vital data, BMI (weight (KG)/height (m) ^{2}), general examination, examination of the heart, chest and neurological examination.

3) Routine investigations :

Standard 12 leads ECG

Radiological examinations including X-ray chest and resting echocardiography using ESAOTE XP-10 (ESAOTE BIOMEDICA COROPORATION) equipped with 2.5-5 MHz transducer.

10 ml of overnight fasting blood samples were drawn: 4 ml for routine laboratory investigations including complete blood count (CBC), liver and kidney function tests, fasting blood glucose levels, serum uric acid, erythrocyte sedimentation rate, lipogram including total cholesterol, TG (triglycerides), LDL-C(low density lipoprotein-cholesterol), HDL-C (high density lipoprotein -cholesterol) in addition to post-prandial blood glucose level detection.

4) Special laboratory investigations:

6 ml blood samples, 3 ml EDTA sample for determination of vitamin C & E and the other 3 ml for detection of serum MDA and sex hormones

Malondialdehyde (MDA); is an end product of fatty acid oxidation that interacts with thiobarbituric acid (TBA) to form a coloured complex that has a maximum absorbance at 532 nm (colourimetric method) (23).

Vitamin E (α-tocopherol); in plasma is oxidized to tocopheryl quinine by $FeCl_3$ and Fe^{+2} in the resultant $FeCl_2$ forms a complex with α, α-dipyridyl to produce a red colour that is read against the blank at 520 nm (24)

Vitamin C (ascorbic acid); in plasma is oxidized by Cu+2 to form dehydroascorbic acid, which reacts with acidic 2,4 dinitrophenyl hydrazine to form a red bis-hydrazone, which is measured at 520 nm (25)

Sex hormones :

Total serum testosterone and total estradiol were determined by electro- chemiluminecent immunoassay through automated auto-analyzer Elecsys 1010 (26). Free serum testosterone was determined by radio immunoassay.

Glycosylated haemoglobin; was determined through human Gmbh (23).

Statistical analysis :

The statistical analysis of the data was done using SPSS (Statistical Package of Social Science) program version 10.

The first part of statistics was descriptive in the form of mean ±standard deviation and frequency & proportion. The second part was analytic for quantitative data (mean ±SD), t-test was used for comparing statistical significant difference between 2 groups. One way ANOVA test was used for more than 2 groups. For qualitative data (frequency & proportion), Chi-square test was used. P value was significant if ≤ 0.05 at a confidence interval 95%.

Table (1) shows that there is a higher level of BMI, SBP, DBP, total cholesterol, TG, LDL-C in cases than in control subjects. HDL-C level is lower in cases than in control subjects.

Table (2) shows that there is a higher level of hemoglobin A1c, total & free testosterone, MDA, morning and nocturnal serum cortisol in cases than in control subjects. In contrast, there is a lower level of total estradiol, ACTH, α-tocopherol and vitamin C in cases than control subjects.

Table (3) shows that the age of the cases was higher in AMI & UA groups in comparison to SA group. BMI is higher in AMI & UA groups in comparison to SA group. BMI is also higher in AMI group in comparison to UA group.

Table (4) shows that there is a higher level of free testosterone, MDA, morning & nocturnal serum cortisol in AMI group in comparison to SA group. ACTH serum level is lower in cases with AMI than in those with SA.

Table (1) The mean & SD of the clinical & routine laboratory data and comparison between cases & control subjects:

Data		Mean	SD	Significance i.e. p-value
Age (ys)	cases	55.8	5.83	0.27
	control	54	5.31	
BMI (kg/m²)	cases	27.42	1.76	0.0001***
	control	23.70	1.22	
Serum creatinine (mg/dl)	cases	1.2	0.52	0.18
	control	1.04	0.15	
SBP (mmHg)	cases	147.83	33.86	0.0001***
	control	131	7.53	
DBP (mm Hg)	cases	96	8.55	0.0001***
	control	82	5.71	
FBG (mg/dl)	cases	141	62.95	0.001**
	control	85.8	10.25	
PPBG (mg/dl)	cases	213.4	107.6	0.0001***
	control	120.4	9.34	
Total cholesterol (mg/dl)	cases	184.93	54.82	0.002**
	control	139.40	36.91	
LDL-C (mg/dl)	cases	111.5	52.97	0.005**
	control	71.5	35.09	
HDL-C (mg/dl)	cases	42.86	6.04	0.016*
	control	46.80	4.44	
TG (mg/dl)	cases	132.73	52.13	0.03*
	control	103.80	30.57	

SD=standard deviation, Ys= years, BMI= body mass index, SBP=systolic blood pressure, DBP= diastolic blood pressure, FBG=fasting blood glucose, PPBG= post-prandial blood glucose, LDL-C=low density lipoprotein-cholesterol, HDL-C=high density lipoprotein-cholesterol,TG=triglycerides,

Table (2): The mean & standard deviation of the special laboratory data and comparison between cases and control subjects:

Data		Mean	SD	Significance i.e p-value
HB A1c (gm/dl)	cases	9.18	2.41	0.0001***
	control	5.40	0.66	
Total testosterone (ng/ml)	cases	1.22	0.65	0.016*
	control	0.81	0.36	
Free testosterone (pg/ml)	cases	4.22	1.68	0.031*
	control	3.14	1.60	
Total estradiol (pg/ml)	cases	13.42	2.83	0.0001***
	control	18.74	0.98	
Morning Cortisol (ug/dl)	cases	16.68	4.06	0.025*
	control	13.91	4.26	
Nocturnal Cortisol (ug/dl)	cases	11.85	3.78	0.02*
	control	9.21	3.80	
ACTH (pg/ml)	cases	80.5	22.79	0.048*
	control	93.3	20.29	
MDA (nmol/ml)	cases	9.72	2.82	0.0001***
	control	3.75	0.75	
α-tocopherol (μmol/L)	cases	17.79	5.97	0.0001***
	control	27.66	3.57	
Vitamin C (μmol/L)	cases	63.86	13.66	0.048*
	control	71.52	12.01	

HBA1c=glycosylated haemoglobin , ACTH=adrenocorticotrophic hormone, MDA=malondialdehyde

Table (3) : The mean & SD of the groups of CAD as regard the clinical & routine laboratory data & comparison between these groups:

Data	Groups	Mean	SD	F	P -value	Special notes
Age (ys)	SA	48	2			
	UA	55.9	5.38	3.69	0.038*	Age of patients with AMI> SA (P 0.011*).It is also higher in UA>SA (P 0.033*).
	AMI	57.11	5.62			
Diabetic duration (ys)	SA	9.6	5.54			
	UA	10.5	6.96	1.34	0.28	
	AMI	15.91	7.08			
BMI (Kg/m2)	SA	23.90	0.60			
	UA	26.93	0.97	19.99	0.0001**	BMI in patients with AMI >SA (P 0.0001***).It is higher in AMI>UA (P 0.005**).It is also higher in UA>SA(P 0.0001)
	AMI	28.33	1.29			
Serum creatinine (mg/dl)	SA	1.03	0.23			
	UA	1.19	0.58	0.19	0.82	
	AMI	1.24	0.53			
SBP (mmHg)	SA	141.66	2.88			
	UA	146.50	7.47	0.66	0.52	
	AMI	149.70	14.52			
DBP (mmHg)	SA	93.33	5.77			
	UA	93.50	5.79	1.01	0.37	
	AMI	97.94	10			
FBG (mg/dl)	SA	129.66	41.73			
	UA	134.90	43.22	0.97	0.39	
	AMI	146.58	78.30			
PPBG (mg/dl)	SA	202.66	81.19			
	UA	211.80	92.72	0.96	0.39	
	AMI	225.05	119.16			
Total cholesterol (mg/dl)	SA	140.66	43.01			
	UA	194.20	54.13	1.14	0.33	
	AMI	187.29	56.04			
HDL-C (mg/dl)	SA	47.33	5.50			
	UA	42.60	5.27	0.91	0.41	
	AMI	42.23	6.52			
LDL-C (mg/dl)	SA	73.66	41.19			
	UA	116.30	50.95	0.84	0.44	
	AMI	115.35	55.81			
TG (mg/dl)	SA	105.66	32.39			
	UA	140	56.82	0.48	0.62	
	AMI	133.23	52.99			

CAD=coronary artery disease, SA=stable angina, UA=unstable angina, AMI=acute myocardial infarction.

Table (4): The mean & SD of the groups of CAD as regard the special laboratory data & comparison between these groups:

Data	Groups	Mean	SD	F	P -value	Special notes
HBA1c	SA	6.23	0.70	2.84	0.07	
	UA	9.67	2.21			
	AMI	9.41	2.42			
Total testosterone (ng/ml)	SA	0.62	0.29	2.49	0.1	
	UA	1.06	0.64			
	AMI	1.41	0.64			
Free testosterone (pg/ml)	SA	2.02	1.62	4.3	0.024*	Free testosterone is higher in patients with AMI > SA (P 0.008**).
	UA	3.98	1.79			
	AMI	4.75	1.32			
Total estradiol (pg/ml)	SA	14.40	1.93	0.18 8	0.83	
	UA	13.27	2.99			
	AMI	13.34	2.97			
Morning cortisol **(ug/dl)**	SA	12.23	1.58	3.21	0.046*	Serum level of morning cortisol is higher in AMI group> SA group (P 0.023*)
	UA	15.89	3.51			
	AMI	17.92	4.11			
Nocturnal cortisol **(ug/dl)**	SA	6.73	1	5.68	0.009**	Serum level of nocturnal cortisol is higher in AMI group > SA group (P 0.004**)
	UA	10.87	2.54			
	AMI	13.27	3.79			
ACTH (pg/ml)	SA	104	1.73	3.66	0.039*	Serum level of ACTH is lower in AMI group < SA group (P 0.023*)
	UA	87.2	14.05			
	AMI	72.41	25.08			
MDA (nmol/ml)	SA	6	0.81	5.32	0.011*	Serum level of MDA is higher in AMI group > SA group (P 0.005**)
	UA	9.03	2.85			
	AMI	10.78	2.39			
α ocopherol **(µ mol/L)**	SA	14.30	3.98	0.59	0.55	
	UA	18.61	6.53			
	AMI	17.92	5.99			
Vitamin C **(µmol/L)**	SA	52.33	5.13	1.26	0.29	
	UA	64.00	13.44			
	AMI	65.82	14.30			

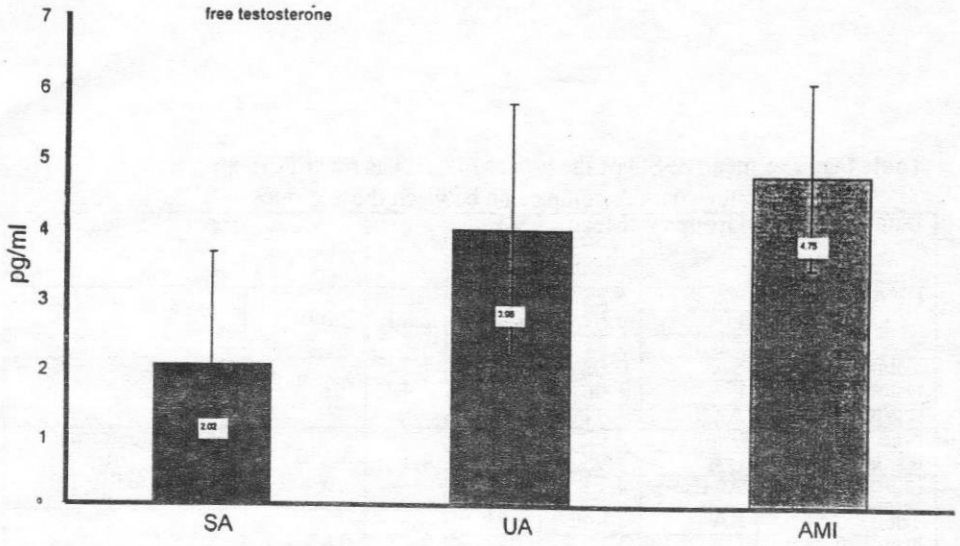

Figure (1): Comparison of free testosterone levels in SA, UA, & AMI groups.

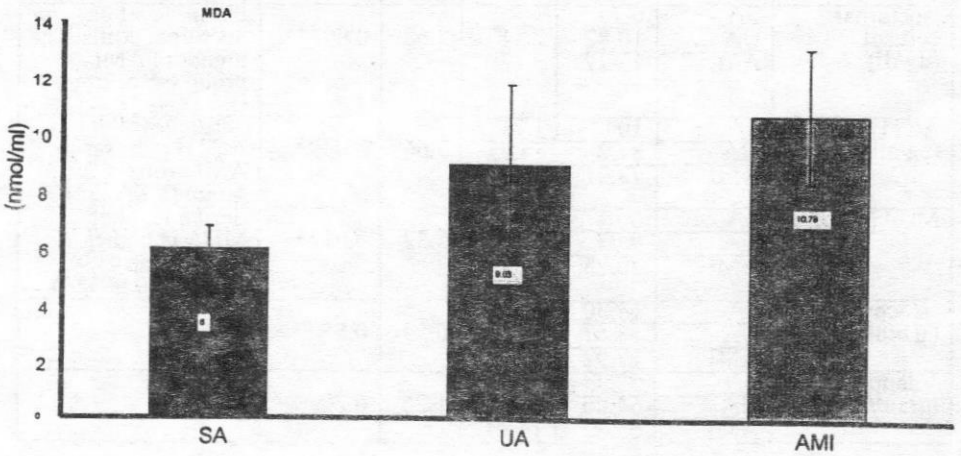

Figure (2): Comparison of MDA levels between the SA, UA & AMI groups.

DISCUSSION

Several lines of indirect evidence suggest that sex hormone levels may be associated with risk of CVD in women. In biologic studies, estrogen has diffuse effects on the CVS, including favorable effects on lipid profiles and fibrinolytic proteins [27], as well as adverse effects on inflammatory and thrombotic markers [28]. Although exogenous hormones have been documented to increase risk of CVD [29], the role of endogenous estrogen level as a risk factor for CVD in postmenopausal women has not been extensively studied.

Testosterone is a potent androgen in women. It is 10- fold more potent than androstenedione and 20-fold more potent than DHEA or DHEA-S. Serum testosterone levels in women are approximately 1/10 th those in men and increases 20-30% at the midcycle due to higher ovarian production [30]. Investigation of patients before and after bilateral oophrectomy provides a paradigm for evaluating the relative contributions of ovaries and adrenal glands to testosterone production in women. Judd et al (1974)[31] reported a 50% decrease in circulating testosterone levels after oophrectomy in postmenopausal women. This suggests that the ovaries account for at least 1/2 of the circulating testosterone levels in postmenopausal women and even a greater proportion in women in reproductive age. Aging results in a reduction of DHEA-S and androstenedione levels in women [32,33], but the effects of age on testosterone in women are controversial [34-36]. However, most studies of total and free testosterone levels after menopause have not demonstrated a persistent decline with advancing age [32,36]. The higher androgen/estrogen ratio has been suggested as a mechanism for increased cardiovascular risk after menopause [37]. High androgen levels may increase cardiovascular risk in women through adverse effects on lipids, blood pressure and glucose metabolism [37,38]

In our study, the BMI of the cases was higher than control subjects ($P< 0.0001$) (table 1). The BMI was significantly higher in AMI group in comparison to SA & UA groups ($P< 0.0001$ & 0.005 respectively) (table 3). Moreover, the BMI was significantly higher

in UA group in comparison to SA group (P<0.0001) (table 2 3). This is in agreement of Robert et al (2003) [39] who had found that in patients with established coronary atherosclerosis, BMI is independently associated with UA and AMI. In contrast, Julio et al (2004) [40] had found that BMI is not a risk factor for UA &AMI in veteran patients with angiographically confirmed CAD. The controversy might be due to the difference in the study population and further prospective large studies are needed to clarify this association.

The SBP and DBP were also higher in cases than in control group (P<0.0001) (table 1). The influence of menopause on blood pressure is controversial. Longitudinal studies have not documented an increase in blood pressure with menopause [41-43], whereas cross-sectional studies had reported significantly higher systolic and diastolic blood pressure in postmenopausal women [44,45]. Staessen and colleagues (1989) [45] reported a fourfold higher prevalence of hypertension in postmenopausal women than in premenopausal women. Studies of endothelial functions using acetylcholine-induced changes in forearm blood flow demonstrated diminished endothelium-dependent vasodilatation in association with menopause, suggesting a role for endogenous estrogen in blood pressure regulation [46]. Hypertension in postmenopausal women is an independent and strong risk factor for CAD [47,48] and acute coronary syndromes [49].

The total cholesterol, TG & LDL-C were significantly higher in cases than control subjects (P 0.002, 0.03 & 0.005 respectively), but the HDL-C was significantly lower (P 0.016) (table 1). This goes with the previous studies that found that the elevated serum levels of total cholesterol, LDL-C & TG as well as lower level of HDL-C are strong and independent risk factors for CAD in women like Gotto et al (2000)[50] & Ballantyne et al (2001)[51]. Bolibar et al (1995) [52] had found a positive correlation between cholesterol level and the degree of coronary stenosis in women diagnosed by coronary angiography.

In our study, the serum levels of total and free testosterone were sig-

nificantly higher in cases than control subjects (P-value 0.016 & 0.031 respectively) (table 2). This agrees with Kim et al (2005) [53] who found a strong association of high FAI and low SHBG (sex hormone binding globulin) with cardiovascular risk factors in peri-menopausal women. Gerald et al (1997) [5] had found a positive relationship between the serum level of free testosterone and the degree of CAD detected by diagnostic coronary angiography. Kathryn et al (2003) [4] had stated that among non-hormone replacement users, lower SHBG and higher FAI levels were noted among postmenopausal women who developed CVD events, but this was not independent of BMI and other CVS risk factors. In contrast to this study, Agnieszka et al (2003) [6] had found that a decreased testosterone level in postmenopausal women is associated with CAD independent of other CAD metabolic risk factors.

Bernini et al (1999) [54] and Golden et al (2002) [55] had found an inverse correlation of serum testosterone with carotid IMT in postmenopausal women. The increased intimal-medial thickness (IMT) is said to be positively correlated with coronary atherosclerosis (O'leary et al, 1999) [56].

Bernini et al (1999) [54] had found that in women, the serum DHEA-S and androgens decline with age and that normal hormonal levels were not associated with major CVS risk factors. They also showed that higher DHEA-S and androgen concentrations were related to lower carotid wall thickness independent of CVS risk factors. Higher testosterone levels in women have been associated with dyslipidaemia [38] as well as type 2 DM [57] and hypertension [58].

We found also that the serum level of free testosterone was significantly higher in cases of AMI than in cases of SA (P-value 0.008)(table 4 and figure 1). This agrees with Kathryn et al (2003) [4] and Guthrie et al (2004) (59) who found a higher incidence of acute coronary syndromes in postmenopausal women not using hormone replacement therapy with high FAI (which is correlated with free testosterone level).

In the present work, the serum level of total estradiol was significantly lower in cases than control subjects (P<0.0001) (table 2). However, it was not significantly different between the clinical groups of CAD (P-value 0.83) (table 4). Kathryn et al (2003) [4] had failed to find an association between the serum level of estradiol and acute cardiovascular events in postmenopausal women. Moreover, the exogenous estrogen hormone given to postmenopausal women had been documented to increase the risk of CAD [29]

We found that morning and nocturnal serum cortisol levels were mildly significant higher in cases than control subjects (P-value 0.025 & 0.02 respectively), and ACTH was mildly significant lower in cases than in control subjects (P-value 0.048) (table 2). Moreover, the morning and nocturnal serum cortisol levels were significantly higher in AMI group in comparison to SA group (P-value 0.023 & 0.004 respectively) (table 4) and the serum level of ACTH was mildly significant lower in AMI group in comparison to SA group (P-value 0.023) (table 4). Jenny et al (2002) [60] had found that cortisol was independently related to coronary stenosis in middle aged women with acute coronary syndrome. The influence of cortisol was important compared to standard risk factors of CAD.

Oxidatively modified LDL-C (ox LDL) plays an important role in the development of atherosclerosis as its uptake by macrophages and smooth muscle cells leads to formation of foam cells which is a critical step in the evolution of the pathological state (61). Circulating ox- LDL and MDA, a lipid peroxidation may therefore reflect the state of pathologic atherosclerosis and may be a possible biochemical risk marker for CAD [62].

In our study, the serum level of MDA was significantly higher in cases than control subjects (P<0.0001) (table 2). Moreover, the serum level of MDA was significantly higher in AMI group in comparison to SA group (P-value 0.005) (table 4). This goes with Amaki et al (2004) [62] who stated that circulating malondialdehyde modified LDL, is a biochemical risk marker for CAD and goes also with Ehara (2002) (63) who found a higher serum

level of MDA in patients of acute coronary syndromes more than in cases with stable CAD.

Vitamin E is a lipid soluble peroxyl radical scavenger in human cells. There are 2 principal forms of Vitamin E; α and γ forms. α-tocopherol predominates in the circulation and is the major form of vitamin E in supplements, which reduces circulating γ-tocopherol levels [64]. α-tocopherol, the most potent antioxidant form of vitamin E, is bound mainly to lipoproteins in plasma, its incorporation into the vascular wall prevents the endothelial dysfunction at an early stage of atherosclerosis [65]. Vitamin E interrupts lipid peroxidation by scavenging peroxyl radical intermediates. Vitamin E may inhibit cell mediated LDL-C oxidation by reducing cellular production and release of reactive oxygen species. Beneficial effects of vitamin E include inhibition of smooth muscle cell proliferation, preservation of endothelial function, inhibition of monocyte-endothelial adhesion, inhibition of monocyte reactive oxygen species and cytokine release, inhibition of platelet adhesion and aggregation, protection of LDL-C against oxidation, increased resistance of LDL-C to oxidation as well as, lowering of cytotoxicity of oxidized LDL-C towards endothelial cells [66-68].

In the present work, α-tocopherol was significantly lower in cases than control subjects (P<0.0001) (table 2), but, there is no significant difference in its level between the clinical groups of CAD (P-value 0.559) (table 4). This may go with Rajasekhar et al (2004) [69] who found that deficiency of vitamin E may be an independent risk factor for CAD in South Indian population and Arcangelo et al (2002) [70] who found an inverse correlation between the plasma concentration of vitamin E and pre-clinical carotid atherosclerosis in middle-aged women and this association was independent of other cardiovascular risk factors and was not related to vitamin supplements. On the contrary, in a large prospective study on blood levels of Vitamin E and CAD, there was no association with CAD in a high risk population (Evans et al, 1998) [71]. In spite of the strong biological rationale for a fundamental role of oxidative stress in atherosclerosis and the supportive epidemiological data, random-

ized clinical trials have overall, with few exceptions, failed to detect clear benefits of vitamin E supplementation on the progression of atherosclerotic lesions or on clinical cardiovascular events [72-74]. Intake of 400 IU/day of RRR- α-tocopheryl acetate for an average of 4.5 years to people with diabetes and at high risk for CV events had a neutral effect on CV outcomes, on microvascular complications, and on glycemic control [75,76]. Several explanations have been proposed for the observed lack of benefit with vitamin E in large trials. Steinberg hypothesized that the effect of antioxidants in atherosclerosis is exerted primarily on early lesions and may be difficult to detect in middle-aged and elderly individuals with advanced disease, and that trials of longer duration than those designed to test pharmacological interventions may be required [77]. Experimental data suggest that vitamin E can become pro-oxidative and that combined antioxidant vitamins can reduce the HDL_2-cholesterol subfraction [74]. Vitamin C (ascorbic acid) is a water soluble vitamin. It has a beneficial effect on the vascular endothelium as it increases the endothelial nitric oxide (NO) by protecting it from oxidation and increasing its synthesis [79,80]. Low plasma vitamin C concentrations have been associated with hypertension and impaired endothelial function. Vitamin C present in fruits and vegetables may protect NO from oxidation and ameliorates endothelial dysfunction. This might account for some of the protective effects of fruits and vegetables on CVS. Pharmacological doses of vitamin C produce vasodilatation in the brachial and coronary arteries [81,82]. In healthy subjects, vitamin C administration restored endothelium- dependent vasodilatation that was impaired by acute hyperglycemia [83]. Thus, vitamin C may have favorable effects on vascular dilatation, possibly through its antioxidant effects on NO [84,85], but these findings are not consistent [86]. Whether vasodilatation occurs at physiologically relevant concentrations of vitamin C is uncertain [87].

We found that vitamin C was mildly significant lower in cases than control subjects (P-value 0.048) (table 2). However, there was no significant difference in its level between the clinical groups of CAD (P-value 0.298)

(table 4). This may go with Gey et al (1993) [88] and Levy et al (1994) (89) who demonstrated an inverse correlation between the plasma levels of vitamin C and CAD. Ram et al (1995) [90] had demonstrated that reduction of plasma levels of vitamin C, E & A and β-carotene was associated with increased risk of CAD among the Indian elderly population. Ram and his colleagues (1996) [91] had found that a combined treatment with antioxidant vitamins A, C, E, and β-carotene in patients with recent AMI may be protective against cardiac necrosis and oxidative stress and could be beneficial in preventing complications and cardiac events rate in such patients. A high vitamin C intake is associated with lower blood pressure [92]. Some studies had shown that supplemented vitamin C intake had lowered blood pressure [93,94]. Catharine et al (2001) [95] had found no significant relation between the plasma concentration of antioxidant vitamins (vitamin C, E) & β-carotene with the intima-media thickness in the elderly women in contrast to men in the same study and the cause of difference was not clear. However, in the same study, women who were using supplements of vitamin E had a smaller mean intima-media thickness and a lower risk of stenosis than did non-users. But these results have to be confirmed with larger well controlled clinical trials using vitamin E & C supplements in postmenopausal women both for primary and secondary prevention of CAD.

SUMMARY AND CONCLUSION

We had found that the serum level of free testosterone was significantly higher in postmenopausal women with CAD than control subjects. The serum level of total estradiol was significantly lower in those women. MDA was significantly higher in them especially those with acute myocardial infarction. On the other hand, the serum levels of anti-oxidant vitamins C & E were lower in those women, but did not significantly differ between the clinical groups of CAD.

We recommend to do large prospective studies including postmenopausal women to delineate the exact relation of sex hormones, MDA and antioxidant vitamins to CAD and acute coronary events and the value of antioxidant vitamin supplements for

primary and secondary prevention of acute coronary syndromes.

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