D-Dimer, A Thrombogenic Marker for Diagnosis of IHD in Menopausal Women

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Abstract: Some haemostatic markers have shown association with IHD, perhaps due to their roles in thrombus formation. These include D-dimer fragment, vWF, and tissue plasminogen activator t-PA. D-dimer is one of the more widely studied hemostatic variables for association with CHD. The present study is focusing on role of biomarker D-dimer in the pathogenesis of IHD in menopausal female. This study involved 76 menopause women suffering from IHD (42 patients with AMI and 34 with angina) and 20 healthy menopause women as control. Patients were divided into subgroups according to the presence of DM and hypertension. Serum D-dimer level is estimated in each group. There is significant reduction in serum D-dimer levels in menopausal women with IHD. Diabetes mellitus and hypertension associated with significant increase in serum D-dimer levels in menopausal women with IHD. Serum D-dimer can be used as biomarker for diagnosis of angina and AMI in menopausal women. Both DM and hypertension have detrimental effect on serum D-dimer levels.

Keywords: D-dimer, IHD, DM, Menopause.

I. INTRODUCTION

Menopause is best defined as the absence of menses for twelve consecutive months. It is a physiologic phase of a woman’s life, result from loss of ovarian function with subsequent deficiency of estrogen hormone. The incidence and prevalence of IHD are higher in menopausal women; hence, various available and prospective markers in relation to menopausal IHD risk were analyzed (1). Women account for 52% of all deaths due to heart diseases, among the female patients who die suddenly from coronary heart attacks, 64% have had no previous symptoms (2). The role of the natural menopause on cardiovascular disease is unclear. Several studies have reported adverse effects of the menopause on cardiovascular risk factors such as lipid profiles, blood pressure, reduced glucose tolerance, obesity, endothelial dysfunction, and vascular inflammation. However, it is difficult to distinguish a discrete effect of the menopause on cardiovascular risk from age-related effects (3, 4). Coronary heart disease (also known as coronary artery disease or ischemic heart disease) is the most common form of heart disease and results from atherosclerosis (5).

Atherosclerosis is a disease characterized by the formation of thickenings of the innermost layer of the arterial wall. These thickenings or atherosclerotic plaques develop in large and medium-sized arteries preferentially at sites with turbulent flow, typical of bifurcations, and curvatures. Atherosclerotic lesions are characterized by inflammation, lipid accumulation, cell death and fibrosis. Clinical complications of atherosclerosis may arise from flow-limiting stenosis, but most of the fatal clinical events are caused by the rupture of a plaque (6). Current major IHD risk factors are male sex, increasing age, family history, smoking habit, presence of diabetes, obesity (especially high levels of visceral adiposity), hypertension, hyperlipidemia and a sedentary lifestyle. Most of these risk factors interrelate in some way either directly or indirectly (7, 8). Some haemostatic markers have also shown association with incident IHD, perhaps due to their roles in thrombus formation, longevity and degradation. These include fibrin D-dimer fragment (9), von Willebrand factor vWF (10), and tissue plasminogen activator t-PA (11). D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross-linked D fragments of the fibrinogen protein (12).

Since its introduction in the 1990s, D-dimer has become an important test performed in patients suspected of thrombotic disorders (13). D-dimer is one of the more widely studied hemostatic variables for association with CHD. Increased D-dimer levels indicate increased fibrin turnover. As for fibrinogen, a number of prospective studies have shown associations with incident CHD events. D-dimer has also been associated with the risk of future IHD; a recent meta-analysis found a combined risk ratio for IHD (after adjustment for other risk factors) of 1.8 (95% CI, 1.4 to 2.4) (14). D-dimer has gained increasing interest for several reasons. First, it can be considered as a global marker of the turnover of cross-linked fibrin and of activation of the hemostatic system. Second, in contrast to several other markers of hemostasis, D-dimer assays are more stable and
more practical to measure and therefore may be more suitable for routine clinical and epidemiological purposes\(^{(15)}\).

**II. PATIENTS AND METHODS**

This is a case control study involved seventy six menopause women, diagnosed by history of amenorrhea for at least twelve months, aged 50-70 years (58±6.3 yr), with clinical evidence of IHD in form of angina (34 patients) or acute myocardial infarction (AMI) (42 patients). Diagnosis of angina and myocardial infarction was based on typical chest pain, positive ECG change, and positive cardiac markers estimation. The patients were collected from the coronary care unit (CCU) in Al-Sadder Teaching Hospital, in Al-Najaf Al-Asrshaf, during the period from January to August 2012. Menopausal women with angina were further classified in to women with DM (16 patients), without DM (18 patients), hypertensive women (15 patients) and normotensive women (19 patients). Menopausal women with AMI were also classified into diabetics (23 patients), non-diabetics (19 patients), hypertensive (20 patients), and normotensive (22 patients). The study also involved twenty menopause women, without evidence of IHD, aged 49- 65 years (55±4.5yr), as control group. Both patients and control women are informed about the study and consent is ensured. All participants are exposed to questionnaire about age, chest pain, history of admission to CCU, smoking, history of hypertension and diabetes mellitus, and drug history. Blood samples were drawn by trained nurses within 24 hours from admission, and sent for baseline investigations, as well as samples of sera were kept freezing at -20°C for estimation of serum D-dimer. Exclusion criteria were smoking, history of estrogen therapy, evidence of renal or hepatic disease. Estimation serum D-dimer is carried out by specific kit for test, supplied by (CUSABIO BIOTECH CO., LTD.USA-Catalog No. CSB-E05175H).

**III. STATISTICAL ANALYSIS**

Data are presented as the mean ± standard error (SE). t-test was used for statistical analysis, p-value < 0.05 was considered significant.

**A. Results**

There was significant increase in serum D-dimer levels in menopausal women with IHD (AMI and angina) compared to healthy menopause women. Table 1. Study of serum D-dimer levels in diabetic menopausal women compared to non-diabetic menopausal women for both AMI and angina group. Table 2. Study of serum D-dimer levels in relation to hypertension, revealed significant increase in serum D-dimer levels in hypertensive menopausal women compared to normotensive menopausal women in AMI group, but not significant in angina group. Table3.

**Table 1: Serum D-dimer levels in menopausal women with IHD (AMI and angina) and healthy menopausal women**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Serum D-dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal women with AMI</td>
<td>232.33±7.44 ng/ml</td>
</tr>
<tr>
<td>(n = 42)</td>
<td></td>
</tr>
<tr>
<td>Menopausal women with angina</td>
<td>200.66±4.03 ng/ml</td>
</tr>
<tr>
<td>(n = 34)</td>
<td></td>
</tr>
<tr>
<td>Healthy menopause</td>
<td>64.04±2.31 ng/ml</td>
</tr>
<tr>
<td>(n = 20)</td>
<td></td>
</tr>
</tbody>
</table>

*p-value < 0.05

**Conclusions**

D-dimer can be used as biomarker for diagnosis of angina and AMI in menopausal women. DM and hypertension have detrimental effect on serum D-dimer levels.

**Table 2: Serum D-dimer levels in diabetic and non-diabetic menopausal women with (AMI and angina)**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Diabetic Women</th>
<th>Non-diabetic women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal women with AMI</td>
<td>254.63 ±5.82 ng/ml (n = 23)</td>
<td>235.61 ±5.62 ng/ml (n = 19)*</td>
</tr>
<tr>
<td>Menopausal women with angina</td>
<td>210.16 ±2.31 ng/ml (n = 16)</td>
<td>204.63 ±2.18 ng/ml (n = 18)**</td>
</tr>
</tbody>
</table>

*p-value < 0.05 ** p-value < 0.05

**Table 3: Serum D-dimer levels in hypertensive and normotensive menopausal women with(AMI and angina)**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Hypertensive women</th>
<th>Normotensive women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal women with AMI</td>
<td>224.51 ±4.23 ng/ml (n = 20)</td>
<td>215 ±2.20 ng/ml (n = 22)*</td>
</tr>
<tr>
<td>Menopausal women with angina</td>
<td>191.14 ±2.81 ng/ml (n = 15)</td>
<td>191.21 ±2.66 ng/ml (n = 19)**</td>
</tr>
</tbody>
</table>

*p-value < 0.05 ** p-value > 0.05

**B. Discussion**

In this study there was a significant increase in D-Dimer levels in menopausal patients with IHD compared to healthy menopause, this result is agreed with Wolfgang et al, who found that increased levels of D-dimer are indicative of a hypercoagulable state, as found in acute coronary syndromes\(^{(15)}\). Gordon et al. suggest that, D-dimer may be a stronger predictor of coronary risk than inflammatory markers, perhaps through its ability to stimulate monocyte release of IL-6\(^{(16)}\). The measurement of circulating levels of tPA and D-dimer may improve the risk stratification of individuals who appear to be at low risk in terms of routinely measured cardiovascular risk factors\(^{(17)}\). The present study showed significant association between elevated D-dimer levels and DM in menopausal women with IHD, this finding is in accordance with Joseph et al, who concluded that insulin resistance in type II diabetes mellitus together with elevated levels of tPA antigen and D-dimer associated with the development and progression of atherothrombotic vascular disease\(^{(18)}\). In the current study there was significant association between elevated D-dimer levels and hypertension in menopausal women with AMI. Coban et al\(^{(19)}\) and Leonardo et al\(^{(20)}\) have reported a strong and independent association between fibrinogen and the presence and severity of hypertension and D-dimer concentrations were significantly related to the severity of target organ damage in IHD hypertensive patients and that hypertension per se may confer a hypercoagulable state, suggest that elevation of D-dimer ,the principle breakdown fragment of fibrin and a reliable indicator of the overall state of activation of the coagulation pathways, is associated with increased risk of future myocardial infarction.

**IV. CONCLUSIONS**

D-dimer can be used as biomarker for diagnosis of angina and AMI in menopausal women. DM and hypertension have detrimental effect on serum D-dimer levels.
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V. RECOMMENDATION

Study Serum D-dimer levels in patients with IHD of different sex and in different age groups.

VI. REFERENCES

[8] Paul W. Inflammatory markers as novel predictors of cardiovascular disease, Thesis for the degree of PhD for M.D, Faculty of Medicine, Division of Cardiovascular and Medical Sciences. 2008; p18-20,37.