Diabetic Foot Ulcer is a Significant Predictor of Silent Myocardial Ischemia in Women with Type 2 Diabetes

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Abstract

Introduction: Screening silent myocardial ischemia in asymptomatic patients with type 2 diabetes is still controversial. The purpose of the present study was to define the value of diabetic foot ulcer (DFU) in the prediction of silent myocardial ischemia in asymptomatic men and women with type 2 diabetes.

Methods: We performed a cross sectional study on 150 diabetic patients with DFU, as cases, and 90 diabetic patients, without the history of any type of DFU, as controls. Presence of silent myocardial ischemia was assessed by dipyridamole single-photon emission-computed tomography myocardial perfusion (SPECT) imaging with thallium-201.

Results: Patients with DFU had longer diabetes duration, higher serum HbA1C, and lower serum high density lipoprotein cholesterol levels, compared to patients without DFU. There were a greater number of women with silent myocardial ischemia (28/63 (44.4%) vs. 28/87 (32.2%); p<0.05) in patients with DFU compared to men. There were a greater number of men with silent myocardial ischemia compared to women (10/47 (21.3%) vs. 2/43 (4.7%); p<0.05) in patients without DFU. Logistic regression analysis demonstrated that the odds ratio of having silent myocardial ischemia was 2.96 in women with DFU, 0.18 in women without DFU and 1.75 in men with DFU compared to men without DFU, adjusting for HbA1c, HDL-C and diabetes duration.

Discussion: Women with DFU are at an increased risk of having silent myocardial ischemia, compared to male counterparts.

Keywords: Diabetic foot ulcer; SPECT; Scan sex characteristics

Abbreviation: BMI: Body Mass Index; SPECT: Single Photon Emission Computed Tomography; TG: Triglyceride; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; SEM: Standard Error of Mean

Introduction

Silent myocardial ischemia is more frequent among type 2 diabetic patients than in non diabetic matched controls [1]. In addition silent myocardial ischemia has a higher predictive value for cardiovascular events than the classical cardiovascular risk factors [2]. There is increasing evidence that intensive medical therapy indicated in diabetic patients at high risk of cardiovascular disorders is as effective as invasive revascularization [3]. Consistently silent myocardial ischemia in patients with type 2 diabetes may reverse over time [4]. There is 80% risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes at high cardiovascular risk [5]. So it is advisable to detect coronary artery disease at the silent stage to prevent cardiac events. However screening all patients with type 2 diabetes for silent ischemia may collapse the health care system. Recent studies try to establish clinical markers for the prediction of silent myocardial ischemia in patients with type 2 diabetes.

Diabetic retinopathy and urinary albumin excretion are known predictors of silent myocardial ischemia, which have a stronger predictive value in men with type 2 diabetes [6,7]. To date we are unaware of any study demonstrating the value of diabetic foot ulcer (DFU) in the prediction of silent myocardial ischemia among patients with type 2 diabetes. The diversity in risk factors for development of coronary heart disease such as dyslipidemia and albuminuria between men and women with type 2 diabetes may had confounded previous studies [8,9]. The purpose of the present study was to define the value of DFU in the prediction of silent myocardial ischemia in asymptomatic men and women with type 2 diabetes.

Method

We performed a cross sectional study on 150 diabetic patients with DFU, as cases and 90 age and body mass index (BMI) matched diabetic patients without the history of any type of diabetic foot disease as controls. Participants were recruited from diabetes clinic of Vali Asr hospital affiliated with Tehran University of Medical Science from January 2008 to December 2010. Diabetes was diagnosed according to the criteria of the American Diabetes Association [10]. Exclusion criteria were type 1 diabetes, acute or chronic renal failure, glumerulonephritis, angina pectoris or angina equivalent symptoms, electrocardiographic evidence of Q-wave myocardial infarction, ischemic ST-segment or T-wave changes, complete left bundle branch block, indications for
We studied the presence of silent myocardial ischemia with dipyridamole single photon emission computed tomography (Dipyridamole SPECT) in cases and controls. Rest-dipyridamole SPECT is the preferred method for the detection of silent myocardial ischemia in patients with type 2 diabetes [13]. Moreover, cases with and without DFU were unable to undergo exercise SPECT. After 30 minutes resting injection of 8 mCi of 99Tc tetrofosmin (Myoview, Amersham, UK) resting images were obtained using ADAC Forte. Three hours later, patients underwent a standard Dipyridamole stress protocol (0.56 mg/kg given intravenously over four minutes) [13]. Stress phase imaging was performed 30-60 min following tracer injection 25 mCi of dipyridamole at peak pharmacological stress (64 views over 180°).

**Blood samples**

Blood samples were collected after almost 12 hours of fasting and, serum creatinine, fasting blood sugar, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and HbA1C were measured. Glucose measurements (intra-assay coefficient of variants [CV] 2.1%, inter-assay CV 2.6%) were carried out using the glucose oxidase method. Creatinine was measured using calibrated Jaffé method (Parsazmoon, Karaj, Iran). Cholesterol, HDL-C, LDL-C and TG were determined using direct enzymatic methods (Parsazmun, Karaj, Iran). HbA1C was estimated by High-Pressure Liquid Chromatography (HPLC) Method. Serum creatinine was measured using direct colorimetric method. White Blood Cell (WBC) count was measured using Sysmex XT-1800i cell counter, Japan.

**Table 1:** Presenting the primary characteristics of participants.

<table>
<thead>
<tr>
<th></th>
<th>Without diabetic foot ulcer (n=90)</th>
<th>With diabetic foot ulcer (n=150)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.8±1.09</td>
<td>56.1±1.97</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes Duration (years)</td>
<td>8.2±0.97</td>
<td>13.2±1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>43 (47.8%)</td>
<td>63 (42.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4±0.75</td>
<td>28.3±0.94</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>145.3±4.50</td>
<td>139.0±4.97</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>87.4±1.96</td>
<td>84.6±2.97</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.9±0.26</td>
<td>8.95±0.37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>165.0±9.61</td>
<td>199.6±26.05</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>191.0±6.163</td>
<td>187.0±6.96</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>106.6±5.4</td>
<td>102.9±5.86</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>50.1±2.24</td>
<td>42.1±2.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>White Blood Cell (per µL)</td>
<td>9920.0±3634.35</td>
<td>1020.7±991.618</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.04±0.048</td>
<td>1.3±0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Silent myocardial ischemia</td>
<td>12 (13.3%)</td>
<td>56 (37.3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Groups are matched for age and BMI. Quantitative variables are expressed as Mean ± Standard Error of mean (SEM); otherwise number and percent. BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NS, none significant.
Results

Demographic, biochemical and clinical characteristics of participants are illustrated in Table 1. The frequency of insulin therapy was 20% (30/150) in patients with DFU and 23% (21/90) in patients without DFU. Similarly, 46% (110/240) of the patients were on statin therapy and 52% (125/240) were on anti-hypertensive treatment. Patients with DFU had longer diabetes duration, a higher serum HbA1C and a lower a serum HDL levels compared to patients without DFU (Table 1).

To study the distribution of risk factors between men and women, we stratified all the studied population according to gender (Table 2). In the group of patients with DFU, there were a greater number of women with silent myocardial ischemia compared to men (28/87 (32.2%) vs. 10/47 (21.3%); p<0.05) (Table 2). In the group of patients without DFU, there were a greater number of men with silent myocardial ischemia compared to women (10/47 (21.3%) vs. 2/43 (4.7%); p<0.05) (Table 2).

Table 3 presents the number of patients with silent myocardial ischemia, in the studied groups, according to the presence or absence of DFU. Logistic regression analysis demonstrated that the odds ratio of having silent myocardial ischemia was 2.96 in women with DFU, 0.18 in women without DFU and 1.75 in men with DFU compared to men without DFU (Table 4).

Discussion

The main finding of the present study was that silent myocardial ischemia was more prevalent in women than in men with DFU and in men than in women without DFU. Likewise the odds ratio of having silent myocardial ischemia was 2.96 in women with DFU, 0.18 in women without DFU and 1.75 in men with DFU compared to men without DFU. This is the first report of the greater value of DFU in the prediction of silent myocardial ischemia in women with type 2 diabetes.

Women with type 2 diabetes have an increased risk of mortality from cardiovascular disorders compared to men [14]. Hence the sex difference seen in mortality from coronary heart disease in general population is abolished in type 2 diabetes [15]. The traditional risk factors for coronary heart disease such as hypertension, elevated serum cholesterol, smoking habit and diabetes dyslipidemia [16], do not explain the excessive prevalence of coronary heart disease.
among women with diabetes [17,18]. Interestingly we showed that the presence of DFU is a significant predictor of silent myocardial ischemia in women only. These results raise the question whether there are different conditions in type 2 diabetic men and women that lead to diabetic complications.

Neuropathy, angiopathy and immunopathy are the key components responsible for DFU complications [19,20]. In 1987, Borch-Johnsen et al. described a male preponderance for the development of severe microvascular complications [21]. It is shown that nitric oxide (NO) bioavailability and NO responsiveness are greater in women than in men with sickle cell disease [22]. In the forearm circulation, stimulated endothelium dependent vasodilatation is greater in female than male patients with diabetes [23]. Consistently Schneider et al. showed that NO availability in the renal circulation is greater in female than in male patients with type 2 diabetes [24]. On the other hand impairment of the microcirculation is believed to play a prominent role in the development of neuropathy [25,26]. It is shown that vasodilatory response of the cutaneous microcirculation of the foot is lower than that of the forearm in healthy subjects and that it progressively worsens in diabetic patients, being lower in patients with neuropathy [27]. Studies suggest that micro-vascular impairment is an early predictor of vascular disease, both in diabetic and non-diabetic patients [28,29]. We therefore concluded that women are usually protected against peripheral arterial disease; and as a consequence are protected against diabetic neuropathy. So once deleterious conditions are strong enough to result into DFU in women with type 2 diabetes, they have had their harmful effect on coronaries long before. In consistent with this hypothesis, Aaberg et al. showed that men with type 2 diabetes develop neuropathy earlier than did the women [30]. Dinh et al. showed a lower risk of developing DFU in women with type 2 diabetes, as a result of less severe neuropathy, increased joint mobility, and lower foot pressures [31]. Height is one of the main predictors for development of neuropathy [32]. As men are taller than women on average, it could be concluded that they are more vulnerable to develop diabetic neuropathy and foot ulcer disease as a consequence. Consistently Dinh et al. showed that once neuropathy or other risk factors are established, women have the same risk of developing foot ulcerations as men [31]. Similar to our findings; Forst et al. showed that limited joint mobility is significantly correlated with intima media thickness and early atherosclerosis only in women with type 1 diabetes, whereas these complications were similarly distributed in male counterparts [33].

On the other hand this may be due to the deleterious role of estrogen in women with type 2 diabetes. White et al. suggested that diabetic state is associated with estrogen-stimulated production of superoxide and a reduced level of NO within the vasculature [34]. Hidden confounders’ for example life style differences between men and women that have not been included in the studied variables may account for the difference as well. Consistently Larkin et al. suggested that risk reducing measures such as taking medications; are underused in women with both type 1 and type 2 diabetes [35]. Furthermore cigarette smoking , which is 5 times more prevalent among Iranian men compared to women [10], is associated with reduced peripheral microvascular responses to both endothelial and smooth muscle cell stimulation [36], as well as blunted basal and stimulated NO bioactivity [37].

The occurrence of risk factors for the progression of DFU depend on metabolic control [38]. Age, BMI, blood pressure, lipid profile and HbA1c did not differ between both sexes at the time of the examination, so it is unlikely that our results are confounded by differences in metabolic control. However, we could not refer to earlier metabolic parameters of our patients, so we could not rule out that the long-term metabolic control could have differed between the men and women.

The limitation of the study are those inherent in a cross sectional analysis which preclude the determination of the direction of causality. Moreover we could not measure transcutaneous oxygen pressure as this instrument was not available in our hospital. So the neuroischemic foot ulcerations may play an importance role in these findings and may have confounded our results. This may imply that peripheral artery disease may be the real predictor of SMI in women. However we took advantage of a relatively large sample size and close similarity between groups in most of the confounding variables. Furthermore silent myocardial ischemia was diagnosed with rest-dipyridamole SPECT, which is the most sensitive non invasive screening test for the detection of silent myocardial ischemia in patients with type 2 diabetes according to the guidelines of American College of Cardiology [13]. We did not used dobutamine stress echography as it is not as sensitive as rest-dipyridamole SPECT and we would miss the patients with silent myocardial ischemia [39]. Silent myocardial ischemia was not confirmed by angiography, due to ethical limitations.

In conclusion we showed that women with DFU are at an increased risk of having silent myocardial ischemia, compared to male counterparts. In a recent study by Gazzaruso and collaborators, erectile dysfunction was considered as an early marker of silent myocardial ischemia in men with type 2 diabetes [40]. Considering the fact that about 40% of patients with asymptomatic coronary artery disease are missed on the basis of current guidelines [41], we suggest diabetic foot ulcer as an early and sensitive risk factor, predicting silent myocardial ischemia in women with type 2 diabetes. Considering the impact of sex steroid hormones on metabolic risk factors, we suggest that diabetes induced complications are mediated by different pathways in men and women.

References


