Erectile dysfunction as a sentinel marker of endothelial dysfunction disease

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ABSTRACT

Introduction: Vascular disease is the major underlying cause of erectile dysfunction (ED). Endothelial dysfunction acts as a marker of "peripheral vascular disease" that occurs prior to clinical vascular disease. ED is the first clinical manifestation of endothelial disease due to the small size of the penile artery. Brachial flow-mediated vasodilation (FMD) is one of the accurate tests for evaluating endothelial function. We compared the endothelial function by FMD between ED patients without clinical signs of vascular disease and non-ED patients.

Methods: 41 ED patients and 30 age-matched normal control subjects were assessed for cardiovascular risks and endothelial function. We measured the FMD in order to evaluate the endothelial function, by comparing the percentage change of the brachial arterial diameter after the brachial arterial occlusion.

Results: There were no significant differences in baseline characteristics, cardiovascular risks and lipid values between both groups, except that the high-density lipoprotein cholesterol was higher in the control group. The percentage change of the FMD was 8.7 +/− 1.0 percent and 5.1 +/− 0.6 percent in ED patients and control subjects, respectively (p-value is 0.007).

Conclusion: ED is the first clinical presentation of sub-clinical endothelial dysfunction disease prior to the appearance of clinical cardiovascular disease or cardiovascular risk factors. ED can be the sentinel marker of early cardiovascular and other systemic vascular diseases and it should thus be employed in preventive strategies.

Keywords: brachial flow-mediated vasodilation, cardiovascular disease, endothelial dysfunction disease, erectile dysfunction, sentinel marker

Singapore Med J 2009; 50(7): 698-701

INTRODUCTION

Erectile dysfunction (ED) is defined as the recurrent or persistent inability to attain and/or maintain an erection for satisfactory sexual performance.[1] ED affects 37.5%–52% of men between the ages of 40 and 70 years[2-4] and presents in up to 100 million men worldwide.[5] Nitric oxide is important in producing the arterial and venous dilation necessary to attain and sustain an erection. Endothelial dysfunction is related to the loss of nitric oxide bioactivity in the endothelium.[6] Abnormalities of this vasodilator system present in atherosclerosis and play an important role in the pathophysiology of ED.[6] Vascular abnormality of the penile arteries is recognised as the most common cause of ED, accounting for 80% of cases.[7] Endothelial dysfunction acts as a marker of "preclinical vascular disease" that may occur many years prior to clinical vascular disease.[6,7] Most previous clinical studies of ED had focused on patients with multiple risk factors for atherosclerosis or patients with known cardiovascular disease. There is few data available on the vasculature of ED patients who have no other clinical cardiovascular disease. Recent studies have shown that brachial flow-mediated vasodilation (FMD) is a reliable test for evaluation of the endothelial function.[6,8,9] We hypothesise that middle-aged and elderly patients who present with ED have systemic vascular disease, and ED is the first clinical manifestation of this disease. The present study was designed to compare the endothelial function by FMD in ED patients with no other clinical cardiovascular disease and non-ED patients.

METHODS

We studied 41 patients with ED without clinical cardiovascular disease and 30 aged-matched control subjects who underwent evaluation of cardiovascular risk factors and endothelial function. ED patients were recruited from the ED clinic, and control subjects were recruited by advertisement. A multi-component questionnaire was designed to evaluate the sexual function and related issues of each patient or subject. ED was evaluated by using the

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Table I. Baseline characteristics of the ED patients and control subjects.

Demographics	Control subjects (n = 30)	ED patients (n = 41)	p-value
Age (years)	55.0 ± 1.6 (41–73)	55.4 ± 1.2 (41–74)	0.85
Body mass index (kg/m^2)	23.7 ± 0.5 (19.03–29.76)	24.2 ± 0.4 (18.03–33.30)	0.46
Systolic pressure (mmHg)	127.3 ± 2.6 (110–170)	128.2 ± 2.1 (110–170)	0.77
Diastolic pressure (mmHg)	83.0 ± 1.7 (70–110)	81.0 ± 1.4 (60–110)	0.38
IIEF-5 questionnaire	23.7 ± 0.2 (20–25)	11.9 ± 0.6 (3–19)	< 0.001

Data is presented as the mean ± standard deviation (range).
ED: erectile dysfunction; IIEF-5: five-item International Index of Erectile Function

Table II. Study results of the ED patients and control subjects.

Results	Control subjects (n = 30)	ED patients (n = 41)	p-value
Laboratory results			
Glucose (mg/dL)	97.6 ± 2.3 (62–123)	101.9 ± 3.2 (77–216)	0.28
Total cholesterol (mg/dL)	215.9 ± 5.1 (158–278)	209.3 ± 7.6 (120–370)	0.47
Triglycerides (mg/dL)	140.1 ± 15.2 (49–366)	158.4 ± 12.1 (43–338)	0.35
HDL cholesterol (mg/dL)	54.2 ± 1.5 (41–73)	47.8 ± 1.5 (34–77)	0.004
LDL cholesterol (mg/dL)	145.3 ± 5.5 (80–230)	132.3 ± 6.7 (37–199)	0.14
Testosterone (ng/dL)	5.4 ± 0.2 (2.6–8.4)	4.9 ± 0.2 (2.0–8.7)	0.14
Brachial artery vasodilation			
Brachial (baseline) diameter (mm)	4.6 ± 0.1 (3.6–6.2)	4.5 ± 0.1 (3.6–6.1)	0.35
Flow-mediated vasodilation (%)	8.7 ± 1.0 (0.0–25.1)	5.1 ± 0.6 (0.0–16.0)	0.007

Data is presented as the mean value ± standard deviation (range)
HDL: high-density lipoprotein; LDL: low-density lipoprotein

International Index of Erectile Function-5 (IIEF-5), an abbreviated form of the IIEF used to classify the severity of ED, with four items selected from the erectile domain portion of the IIEF and one addressing sexual satisfaction.[10] The degree of ED was classified by the erectile function domain score as severe (1–7), moderate (8–11), mild to moderate (12–16), mild (17–21), or none (22–25). The questionnaires consisted of components to evaluate the history of smoking, hypertension, coronary heart disease, dyslipidaemia, diabetes mellitus and the general medical history including assessing body mass index. Clinical history or physical examination of all ED subjects did not show evidence of cardiovascular disease. Exclusion criteria for ED patients and control subjects included recent history of smoking (in previous five years), known hypertension, coronary heart disease, hyperlipidaemia, diabetes mellitus, and neurogenic, hormonal and psychogenic causes of ED.

The following laboratory tests were performed: fasting lipid panel (cholesterol, triglycerides, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol), fasting glucose, complete blood count, blood urea nitrogen, creatinine, liver function test and serum testosterone. FMD assessment was done as follows: after a ten-minute rest, the assessment of brachial artery vasodilation was done using a high-frequency ultrasonographic scanning probe (11-MHz) to obtain longitudinal images of the brachial artery at a marked point 5–10 cm proximal to the antecubital fossa. A two-dimensional baseline image was obtained with Doppler ultrasonography to assess the arterial diameter, then the arterial occlusion cuff was positioned at the proximal upper extremity. FMD was produced by inflating the cuff to 300 mmHg for five minutes to occlude arterial flow, and the second arterial diameter measurement was then made 90 seconds after cuff deflation. FMD is expressed as the percentage change from the diameter before cuff inflation to the diameter at 90 seconds after cuff deflation.

RESULTS

Patient profiles are shown in Table I. There were no significant differences in the blood tests between the two groups, except the HDL cholesterol levels which were significantly lower in ED patients compared to the controls (47.8 ± 1.5 vs. 54.2 ± 1.5, p = 0.004). Glucose, total cholesterol, triglycerides, LDL cholesterol and testosterone levels were not statistically different between the two groups. There was no significant difference in the baseline brachial diameter between ED patients and the controls (4.5 ± 0.1 mm vs. 4.6 ± 0.1 mm, p = 0.35). FMD was significantly lower in ED patients compared to the control subjects (5.1 ± 0.6 vs. 8.7 ± 1.0, p = 0.007) (Table II).

DISCUSSION

ED has a high prevalence and affects most men between 40 and 70 years of age.[2-4] ED is caused by two main organic and psychogenic aetiologies. ED problems due to organic causes comprise up to 80% of cases, while vascular disease is the most common pathophysiology of ED.[7] The common risk factors for atherosclerosis have been frequently found in patients with ED.[7,11] 64% of men who presented with myocardial infarction had ED prior to their heart problems, and 57% of men undergoing coronary artery bypass graft surgery had ED before the operation.[11] The number of coronary vessels involved is a significant factor in the severity of ED.[12] Endothelial dysfunction that occurs many years prior to vascular disease, such as atherosclerosis, is an early abnormality of the artery. Endothelial dysfunction and atherosclerosis are systemic disorders that affects all major vascular beds.[7]

The link between ED and coronary artery disease (CAD) is further substantiated by a similar pathogenic involvement of nitric oxide (NO) pathways with an impairment of FMD and late structural vascular abnormalities.[8,12] Symptoms of vascular disease depend on the size of arteries supplying various organs, which have different sizes (1–2 mm of the penile artery, 3–4 mm of the proximal left anterior descending (LAD) artery, 5–7 mm of the internal carotid artery and 6–8 mm of the femoral artery).[11] The clinical presentation of atherosclerosis of the penile artery, proximal LAD artery, internal carotid artery and femoral artery are ED, stable and unstable angina/acute myocardial infarction, transient ischaemic attack/stroke, and claudication, respectively.[11] Generally, the threshold for the development of symptoms is reached when the lumen of the artery is occluded by 50%.[11] The first symptom of artery abnormality usually occurs in the penile artery, which is the smallest artery in the body.[11] ED may therefore be considered a clinical manifestation of a disease affecting penile circulation as a part of a more generalised vascular disease or advanced cardiac events.

The penile vascular bed is dependent on NO for vasodilation of the arteries to produce rapid blood inflow and vasodilation of the trabecular smooth muscle of the lacunar space to prevent venous outflow, making the penile vascular bed susceptible to deficiencies of the NO/cyclic guanosine monophosphate (cGMP) vasodilator system.[6] ED patients, who have undergone assessment of FMD and vasodilation to the sublingual nitroglycerin, show peripheral vascular abnormality in the NO/cGMP pathway. FMD is known to be largely mediated by NO, suggesting ED may be the first manifestation of cardiovascular disease caused by an abnormality in the peripheral vascular NO/cGMP vasodilator system. PDE-5 inhibitor treatment results in an amelioration of ED problems that can be explained by an improvement of the NO/cGMP system in erection mechanism.[6] Currently, the most acceptable measurement for assessing endothelial function is brachial artery ultrasonography.[6,13]

The aim of FMD is to increase brachial artery blood flow in response to transient hyperaemia, which is provoked by inducing post-ischaemic dilation of distal vascular beds.[6] The increase of the diameter was less in patients with impaired endothelial function. Reactive hyperaemia was done by inflating a paediatric blood pressure cuff to 200–500 mmHg above systolic blood pressure for five minutes to occlude arterial flow; arterial diameter and flow velocity measurements are made at 60 seconds after cuff deflation.[6] Recent data has shown a strong relationship between abnormal coronary and FMD.[14] Coronary endothelial dysfunction can be assessed by FMD. FMD is also associated with cardiovascular disease and cardiovascular risk factors including smoking, diabetes mellitus, advanced age and hypercholesterolaemia.[15] FMD is nearly as sensitive as exercise electrocardiography in the detection of CAD, and is more specific for diagnosis than exercise electrocardiography.[16] The impairment of FMD (endothelial-dependent vasodilation) was found to represent endothelial dysfunction in ED patients.[6,8,9]

In our study, we found no significant difference in cardiovascular risks between ED patients and non-ED patients, except for the higher HDL cholesterol value in the normal control group. The study of FMD showed a significant difference between the normal control group and the ED group (8.7 ± 1.0 vs. 5.1 ± 0.6), demonstrating endothelial dysfunction in ED patients without clinical cardiovascular risks. This finding confirmed that the patients who developed ED had endothelial dysfunction prior to the clinical symptoms and laboratory tests of cardiovascular risks. In conclusion, ED is the first clinical presentation and marker of generalised endothelial dysfunction, which often appears prior to the appearance of any abnormal cardiovascular risk factors or clinical cardiovascular indications, and can be detected by noninvasive brachial artery ultrasonography at the clinical level.

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