The Triad of Endothelial Dysfunction, Cardiovascular Disease, and Erectile Dysfunction: Clinical Implications

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1. Introduction

Erectile dysfunction (ED) is defined as the inability to reach or maintain erection sufficient for satisfactory sexual performance. Evidence is accumulating in favor of ED as a vascular disorder in the majority of patients. In fact, common risk factors for atherosclerosis have been frequently found in patients...
with ED, and the severity of ED has been related to the number and severity of risk factors themselves [1,2]. Moreover, abnormal sexual function has been reported in patients with vascular diseases such as coronary artery disease (CAD) [3–5], diabetes [2,6], cerebrovascular disease [7], and hypertension and peripheral arterial disease [8,9]. Finally, ED and vascular diseases share a similar pathogenic involvement of nitric oxide (NO)-pathway leading to impairment of endothelium-dependent vasodilation (early phase) and structural vascular abnormalities (late phase) [10–12]. If these observations hold true, ED may be considered to be the clinical manifestation of penile circulation disease that is frequently part of major vascular diseases and that may be an early marker of subclinical atherosclerosis. This paper discusses the clinical evidence supporting the link between endothelial dysfunction, ED, and cardiovascular (CV) disease.

2. Evidence acquisition

A MedLine search of the dates January 1980 to July 2008 was performed that included original and review manuscripts articles with focus on anatomic, physiologic, epidemiologic, and clinical outcomes.

3. Evidence synthesis

3.1. Endothelial dysfunction and cardiovascular disease

Atherosclerotic process begins during childhood, goes through a long asymptomatic phase, and becomes clinically evident from middle age (Fig. 1). Endothelial dysfunction is the first step of atherosclerosis. It is characterized by a reduction of the bioavailability of vasodilators, in particular NO, with a shift toward vasoconstrictors. This imbalance leads to alteration of endothelium-dependent vasodilatation that is the key finding of endothelial dysfunction. In this early phase, vascular imaging frequently shows an entirely normal appearance of the vessel wall, confirming that endothelial dysfunction precedes macroscopic vascular alterations. This step is followed by an intermediate preclinical phase where plaque formation takes place. Due to the compensatory enlargement of the vessel area known as the Glagov phenomenon [13], early plaque can be accommodated without impinging on the lumen artery by distending the external elastic membrane of the arterial wall. While the accumulating plaque burden does not induce flow-limiting obstruction, it may be the cause of acute CV events in predisposed patients [14]. The positive remodeling phenomenon

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**Fig. 1** - The atherosclerotic process is schematically divided into three phases. Each phase is characterized by a given pathophysiologic substrate and related vascular disease (ie, vascular images are drawn from coronary circulation by intravascular ultrasound) and by a specific clinical setting (ie, number of risk factors per patient, severity of sexual dysfunction, and reversibility of the disease). The diagnostic tests to address each step are indicated.
continues until 40% of the lumen artery is encroached by plaque. At that time, any further plaque growth will narrow the lumen artery, which represents the beginning of the late phase of atherosclerosis. This step is characterized by obstructive vascular changes, leading to symptomatic vascular disease. Endothelial dysfunction is still an important factor in this late step of the disease contributing to the genesis of myocardial ischemia and acute coronary syndromes through changes in plaque compositions that ultimately may influence plaque stability [15].

The magnitude and the speed of development of the atherosclerotic process is the result of a complex interplay of genetic, environmental, biochemical, and mechanical factors. The patient’s risk-factor profile is a key variable in the pathogenesis of endothelial dysfunction. Previous studies have shown that the extent of endothelial dysfunction was related to the number of traditional risk factors regardless of the method used to test endothelium integrity and the vascular bed (coronary or peripheral circulation) [16,17]. Moreover, impairment of the endothelium-dependent dilation has been found to predict long-term coronary events [18,19] in patients with or without obstructive CAD. The treatment of risk factors and vascular conditions associated with endothelial dysfunction (e.g., hypertension, hypercholesterolemia, obesity) has been shown, in at least some studies, to improve long-term prognosis. This is probably due to “stabilization” of nonobstructive atherosclerotic plaques and improvement of endothelium vasomotor response [15,20–23]. These observations support the concept of “reversibility” of the atherosclerotic functional changes by specific interventions targeting endothelial dysfunction. Whether this potential curative effect on endothelium is restricted to or is more evident in the early phase of the atherosclerosis rather than late in the course of the disease is a matter of debate. Thus, the key points for prevention of CV events is the early identification of endothelial dysfunction using noninvasive tests in subjects at risk and the treatment of risk factors combined with changes in lifestyle.

3.1.1. Clinical assessment of endothelial function: endothelium-dependent vasomotion
Endothelial-dependent, flow-mediated dilation has been the most widely used clinical end point to assess endothelial integrity. Initial studies of the coronary circulation were undertaken to assess changes in epicardial artery diameter during intracoronary infusion of acetylcholine [24]. In the presence of normal endothelium, graded doses of the endothelium-dependent substance acetylcholine induced progressive dilation of the coronary artery. In the case of endothelial dysfunction, blunted dilation response or even paradoxical constriction (a direct muscarinic effect on smooth muscle cells) was detected. Since endothelial tests for coronary circulation are invasive and impractical to use on a wide scale, noninvasive evaluation of endothelial function by brachial artery ultrasound has been introduced. The noninvasive determination of the endothelium-dependent and -independent vasodilatation of the brachial artery is performed according to both the method described by Celermajer et al in 1992 [25] and the guidelines for the ultrasound assessment of endothelial-dependent, flow-mediated dilation of the brachial artery [26]. The diameter of the brachial artery is measured by a B-mode ultrasound device positioned 2–15 cm above the elbow, at rest and during reactive hyperemia induced by 5-min occlusion of the brachial artery by an inflated cuff positioned on the forearm (Fig. 2). This results in stress-induced NO release and subsequent vasodilation. The flow-mediated dilation measured by this technique can be blocked by an infusion of N(G)-monomethyl-L-arginine (L-NMMA) [27], a specific antagonist of NO synthase. After 15 min of rest, sublingual nitroglycerine (0.05 mg) is administered, and the test is repeated to assess the endothelium-independent flow-mediated response. Vessel dilation during reactive hyperemia and after nitroglycerine administration are expressed as the percent change in brachial-artery diameter from the baseline value. Results similar to those obtained from invasive studies have been reported, confirming endothelial dysfunction as a systemic disorder [28].

3.1.2. Clinical assessment of endothelial function: circulating markers
Circulating markers of endothelial cell damage have been previously reported in many conditions. They are called activated endothelial cells (EACs), and they basically indicate early development of atherosclerosis. Three categories of EACs are recognized: cytokines and chemokines, soluble adhesion molecules, and acute-phase reactants [29]. Increased plasma concentrations of activated endothelial cells have been found to be associated with risk factors/conditions such as obesity, hypertension, type 2 diabetes [29–32]. While measurement of these circulating markers can provide important information on endothelial function/dysfunction of specific population of patients, their current use is still limited by challenging and expensive assays. Among several circulating markers that directly or
indirectly reflect endothelial dysfunction, data are accumulating on the role of asymmetric dimethylarginine (ADMA) and high-sensitivity C-reactive protein (hsCRP). ADMA is an endogenous inhibitor of NO synthase. There is room to suggest that blockage of NO generation by elevated ADMA levels initiates and facilitates the atherosclerosis process that promotes CV events [33,34]. Increased plasma concentrations have been found to be associated with common risk factors and with early atherosclerosis. Moreover, mobilization, differentiation, and function of endothelial progenitors cells are repressed by ADMA [35].

Although debate persists regarding the precise physiologic role of hsCRPs, the prognostic value of hsCRP as a marker of CV risk is now firmly established. While hsCRP predicts future CV events in many clinical conditions, including healthy subjects without CV disease [36], epidemiologic studies of the general population unselected for CVD have found a poor correlation with results of tests that quantify the extent of atherosclerosis, such as carotid intima-media thickness (IMT) measured by Doppler ultrasound or by coronary calcification measured by electron-beam computed tomography (EBCT). These observations have led some to suggest that elevated hsCRP levels may primarily reflect an increased tendency for plaque rupture rather than a high atherosclerotic burden.

3.2. Endothelial dysfunction and erectile dysfunction

Endothelial dysfunction is a key finding in a patient with ED, particularly in the early phase of the disease. In a later phase, other factors, such as impaired arterial flow of hypogastric/pudendal arteries, cavernosal fibrosis, and hypoxia, come into play to cause and maintain sexual dysfunction [10]. Among several published reports investigating the link between endothelial dysfunction (assessed by circulating markers and/or flow-mediated dilation) and ED (Table 1), three papers provided good descriptions of the concept of endothelial dysfunction as an early, systemic marker of atherosclerosis (Fig. 3). Bocchio et al [37] compared circulating...
markers of endothelial cell activation (vascular cell adhesion molecule–1 [VCAM-1], soluble intercellular adhesion molecule–1 [sICAM-1], endothelin-1 [ET-1], and P-selectin) in 45 patients with ED but without CV risk factors (group 1), in 45 patients with both ED and CV risk factors (group 2), and in a control group of 25 healthy subjects. ED patients with risk factors were further separated into two subgroups, ED with diabetes (group 3) and ED with hypertension (group 4, not shown in the figure). Penile Doppler test was negative in group 1 and positive in groups 2 and 3. Interestingly, measures of endothelial cell activation were significantly higher \((p < 0.01)\) in group 1 compared to the control group. No differences were found among the ED groups. Moreover, ET-1 was the best independent predictor of ED, suggesting that biochemical measures of endothelial damage are detectable early in an ED patient, independent of common risk factors and structural heart disease. Kaiser et al [38] assessed both endothelium-dependent and -independent vasodilation in 30 relatively young subjects (mean age: 46 ± 2 yr).

<table>
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<tr>
<th>Markers</th>
<th>Action</th>
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<tr>
<td>sVCAM-1, sICAM-1, P-Selectin, tPA, PAI-1</td>
<td>Markers of the extent of endothelial cell activation (endothelial damage)</td>
<td>Bocchio et al [37]; Vlachopoulos et al [41]</td>
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<tr>
<td>Endothelin-1</td>
<td>Endogenous vasoconstrictor substance</td>
<td>Bocchio et al [37]; Francavilla S, 1997; Baumhäkel M, 2005</td>
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<tr>
<td>Circulating endothelial progenitors cells</td>
<td>Endothelial endogenous maintenance and repair potential</td>
<td>Bocchio et al [37]; Foresta C, 2006; Foresta C, 2007; Baumhäkel M, 2006</td>
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<tr>
<td>hsCRP, IL-6, IL-1β, TNF-α</td>
<td>Marker of inflammation. Mediators of lesion formation.</td>
<td>Bank AJ, 2003; Giugliano F, 2004; Chiurlia E, 2005; Vlachopoulos et al [41]</td>
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ADMA = asymmetric dimethyl L-arginine; sVCAM = soluble vascular cell adhesion molecule; sICAM = soluble intracellular adhesion molecule; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-α; VWF = von Willebrand factor; tPA = tissue type plasminogen activator; PAI-1 = plasminogen activator inhibitor-1.

Fig. 3 – Comparison of diagnostic methods to test endothelial function in patients with erectile dysfunction: (A) Endothelial cell activation assessment in 25 healthy subjects (control), 45 patients with erectile dysfunction (ED) and no risk factors (group 1), and 45 patients with ED and some risk factors (group 2); ED patients with risk factors were further separated into ED with diabetes (group 3) and ED with hypertension (group 4, not shown in the figure). Penile Doppler test was negative in group 1 and positive in groups 2 and 3. Interestingly, measures of endothelial cell activation were significantly higher \((p < 0.01)\) in group 1 compared to the control group. No differences were found among the ED groups. Moreover, ET-1 was the best independent predictor of ED, suggesting that biochemical measures of endothelial damage are detectable early in an ED patient, independent of common risk factors and structural heart disease. Kaiser et al [38] assessed both endothelium-dependent and -independent vasodilation in 30 relatively young subjects (mean age: 46 ± 2 yr).
with vasculogenic ED (penile Doppler test peak systolic velocity <35 cm/s) but without risk factors or heart disease (ie, carotid IMT by ultrasound, coronary calcification by CT-angiography, and aortic pulse wave velocity) compared with 27 subjects without ED. Baseline characteristics were similar between groups. Brachial artery flow-mediated dilation (1.3% vs 2.4%; \( p = 0.0014 \)) as well as vasodilation to nitroglycerin (13% vs 17%; \( p < 0.05 \)) were significantly lower in ED group compared with non-ED subjects, suggesting a generalized peripheral vascular disease. Finally, Elesber et al [39] investigated coronary endothelial function in 56 men with suspected CAD who were found to have an entirely normal coronary angiogram. Patients were divided in two groups according to normal (\( n = 24 \)) or abnormal (\( n = 32 \)) dilator response to intracoronary infusion of acetylcholine of macro- and microcirculations. Interestingly, patients with endothelial dysfunction had both significantly impaired sexual function by International Index of Erectile Function question 5 (IIEF-5) (mean score: 17 [range: 9.5–22.5]) vs mean score: 22.5 [range: 19–24]; \( p = 0.008 \)) and higher ADMA plasma levels (0.45 ± 0.07 vs 0.50 ± 0.06; \( p = 0.017 \)) compared to men with normal endothelial function. Moreover, endothelial function was correlated with ED scores after adjustment for several confounding variables. The study demonstrated for the first time the association between coronary endothelial dysfunction and an increase of ED prevalence in men without angiographic significant CAD. An increased ADMA plasma concentration may be a potential mechanism of endothelial dysfunction in these patients.

Taken together the results of these studies confirm the role of endothelial dysfunction as early vascular abnormality in ED. This vascular alteration is detectable at the level of both peripheral and coronary circulations and may involve also the endothelium-independent pathway suggesting a generalized vascular smooth-muscle–cell disorder. The patient’s risk-factor profile is not the only determinant of endothelial dysfunction. Low-grade subclinical inflammation has been identified as an additional factor affecting endothelial function in all stages of the atherosclerotic process. Vlachopoulos et al actively investigated the link between inflammation, metabolic syndrome, ED, and CAD [40]. They recently assessed a wide spectrum of inflammatory markers (eg, hsCRP, interleukin 6 [IL-6], interleukin-1 beta [IL-1β], and tumor necrosis factor alpha [TNF-α]) and prothrombotic markers (eg, von Willebrand factor [vWF], plasminogen activator inhibitor type 1 [PAI-1], tissue plasminogen activator [tPA], and fibrinogen) in patients with ED and CAD [41]. They found that these markers/mediators were significantly increased in ED patients both with and without CAD, suggesting that ED adds an incremental inflammatory and endothelial-prothrombotic activation on top of CAD. Interestingly, there was no difference in terms of activation of these mediators between men with either ED or CAD alone. This intriguing finding may suggest, as the authors said, “an inflammatory equivalence” between ED and CAD. If confirmed, these observations would lend support to the concept of ED as a “CAD equivalent” [42]. In other words, asymptomatic middle-aged men with ED and no CV disease should be considered as having a 10-yr CV risk equal to CAD or diabetes (ie, a CV risk >20% or >2% per year according to the Framingham chart of risk). In this case, an “aggressive” diagnostic and therapeutic assessment should be planned for each subject. The algorithm suggesting which target (ie, between nonobstructive and obstructive CAD) should be investigated and which test (ie, direct measure of coronary reserve vs surrogate of atherosclerotic burden) should be considered to be the first step in any patient evaluation have been extensively discussed in previous studies [43,44].

Is ED a reversible disease? Treatment of risk factors commonly associated with ED may lead to improvement of or reversal of sexual dysfunction, probably through a beneficial effect on endothelium vasomotion. Esposito et al reported that lifestyle changes including diet and physical activity improved or reversed ED in obese men at a 2-yr follow-up [45]. Similarly, cessation of smoking and optimal glycemic control [46] were associated with improvement of sexual function. A small study [47] investigated the effect of cholesterol-lowering therapy with atorvastatin in young men with low-density lipoprotein (LDL) cholesterol >120 mg/dl as the only risk factor. Lowering blood lipids improved or normalized sexual function in eight of nine subjects, fueling the concept that the sooner the therapy for risk factors begins and the fewer the number of patient risk factors at baseline, the greater the pharmacologic response to treatment. In this specific setting, the beneficial effect played by statins may be also due to their anti-inflammatory and antithrombotic properties rather than to their cholesterol-reducing effect. What is called a “pleiotropic effect” may ultimately concur in the restoration of normal endothelial function [48]. Finally, drugs that may interfere with sexual function, such as beta-blockers, diuretics, antidepressant agents, and so forth should be replaced with other compounds, and sexual function should be retested after a few weeks.
3.3. Erectile dysfunction and cardiovascular events

Data are accumulating in favor of ED as an independent predictor of future cardiocerebrovascular events compared to subjects without ED. Blumentals et al [49] examined a large cohort of patients (n = 12825) diagnosed with ED and recruited by an administrative database and compared them with a similar number of control subjects without ED. The ED group had a 2-fold increase (OR: 1.99; 95% CI: 1.17–3.38) in the risk of acute myocardial infarction (AMI) compared to non–ED patients after adjusting for age at ED diagnosis, smoking, obesity, and use of medications such as ace inhibitors, beta-blockers, and statins. Study limitations were mainly inherent to the type of database used; it included only patients with established ED and AMI (probably the most severe cases); and it lacked information about potential comorbidity and diabetes. The first prospective, placebo-controlled study assessing the role of “incidental ED” as predictors of CV events was the Prostate Cancer Prevention Trial [50]. Among 9457 subjects aged ≥55 yr enrolled in this study, 4247 had no ED at study entry and were followed up for 5 yr. Onset of both “incidental ED” and CV events (eg, AMI, angina, stroke, congestive heart failure, transient ischemic attack [TIA], or arrhythmias) was monitored. Fifty-seven percent of subjects developed ED over the follow-up period. After adjusting for potential confounders, men with ED had a significantly increased risk of AMI or angina (HR = 1.37; 95% CI, 1.06–1.76; p = 0.02) and any CV events (HR: 1.25; 95% CI: 1.02–1.53; p = 0.04) compared to those without incidental ED (HR: 1.37; CI: 1.06–1.76; p = 0.02). Moreover, a trend for stroke was also noted (HR: 1.70; 95% CI: 0.98–2.96; p = 0.06). ED had an equal or greater effect on subsequent CV events of the same magnitude as that of family history of premature CAD, smoking, or hypercholesterolemia. Two recently published studies confirmed the link between ED and subsequent CV events in type 2 diabetics. Gazzaruso et al [51] investigated 291 type 2 diabetes with angiographically detected silent CAD. Over a mean follow-up of 47 months, patients who developed adverse events were more likely to have ED compared to those who did not (61.2 % vs 36.4%, p = 0.001). Interestingly, the presence of ED added to the already higher risk of major adverse CV events. Ma et al [52] studied 2306 diabetic patients with no clinically manifest CAD. During a median follow-up of 4 yr, the incidence of CAD was higher in men with ED as compared to those without ED (197 of 1000 men per year vs 95 of 1000 men per year). ED remained an independent predictor of CAD (HR: 1.58; 95% CI: 1.08–2.30; p = 0.018) after adjustments were made for age, duration of disease, use of antihypertensive drugs, and albuminuria. Finally, the Krimpen longitudinal study [53] assessed the role of a single question on the severity of ED as a risk indicator for developing future CV events in a population-based cohort of 1248 men without CVD. During a mean follow-up of 6.3 yr, men with reduced or severely reduced erectile rigidity had a hazard ratio of 1.6 (95% CI: 1.2–2.3) and 2.6 (95% CI: 1.3–5.2) for developing future CV events (eg, AMI, sudden death, and stroke), after adjustment for classic risk factors. Thus, a single question on erectile function should be included in each CV office-based assessment in order to improve risk stratification.

4. Conclusions

According to the available literature, each patient developing ED should be considered as a cardiac patient until proven otherwise [44]. Endothelial dysfunction is the key feature in the early phase of ED, whereas it is one of many factors accounting for sexual dysfunction in the late phase of the disease. Evidence is accumulating in favor of ED as an independent predictor of future CV events in patients without overt heart disease. Improvement or even reversal of ED may be obtained through treatment of risk factors combined with specific pharmacologic treatment, particularly if ED is detected early after onset of symptoms. Thus, doctors should more actively ask about ED in each middle-aged man, and patients should be less embarrassed to talk about this problem with their referral physician. Several office-based risk-assessment charts are available to stratify healthy subjects with some risk factors, including ED, into low, intermediate or high CV risk categories. According to each subject score, reassurance (for low risk), additional noninvasive tests (for intermediate risk) or invasive test with treatment (for high risk) should be recommended. Whether ED should be considered as a “CAD equivalent” (ie, similar to diabetes, overt CAD, or extracardiac atherosclerosis, asymptomatic patients with multiple risk factors conferring a 10-yr risk of CAD >20%) is still a matter of debate. While further studies are warranted to fill this gap in research, cardiologic assessment and aggressive treatment of risk factors should be given to each patient complaining of sexual dysfunction.

Conflicts of interest

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References


