Review – Sexual Medicine

Inflammation, Metabolic Syndrome, Erectile Dysfunction, and Coronary Artery Disease: Common Links

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Abstract

Objective: Erectile dysfunction (ED) may be the early clinical manifestation of a generalized vascular disease and carries an independent risk for cardiovascular events. Low-grade subclinical inflammation affects endothelial function and is involved in all stages of the atherosclerotic process. This review identifies potential pathophysiologic links among low-grade inflammation, ED, metabolic syndrome, and coronary artery disease (CAD) and presents the clinical implications in terms of ED diagnosis, assessment of patient risk, and therapy.

Methods: A comprehensive evaluation was performed for available published data in full-length papers that were identified in MedLine up to July 2007.

Results: Studies support an association between metabolic syndrome, ED, and increased inflammatory state. Increased circulating levels of inflammatory and endothelial-prothrombotic compounds are related to the presence and severity of ED. Specific inflammatory biomarkers and their combination appear to have the potential to aid ED diagnosis or exclusion. ED and CAD may confer a similar unfavorable impact on the inflammatory and prothrombotic state, whereas ED adds an incremental activation on top of CAD; these findings have important implications for cardiovascular risk. Lifestyle and risk factor modification, as well as pharmacologic therapy, are associated with anti-inflammatory effects.

Conclusions: Low-grade systemic inflammation could be an important element of the association between metabolic syndrome, ED, and CAD. Its individualized assessment may be a valuable tool for ED diagnosis, risk assessment, and rationalized therapeutic approach especially in patients with ED who have metabolic syndrome and carry an intermediate risk for future cardiovascular events.

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1. Introduction

Longitudinal population-based studies clearly demonstrate that cardiovascular risk factors such as hypertension, dyslipidemia, central obesity, and insulin resistance are major risk factors for vasculogenic erectile dysfunction (ED) as well [1]. Furthermore, recent data suggest that the clustering of these factors, as occurs in patients with metabolic syndrome, increases the risk for the development of ED even further [2,3].

ED may be the early clinical manifestation of a generalized vascular disease and carries an independent risk for cardiovascular events [4,5]. ED is associated with the presence and extent of asymptomatic atherosclerosis, including that of the coronary arteries, and precedes the development of clinically evident coronary artery disease (CAD) by a significant amount of time [6–9]. In angiographically documented CAD, ED rate varies according to type of clinical presentation (acute or chronic) and related atherosclerotic background (single or multivessel disease) [9].

Low-grade subclinical inflammation affects endothelial function and is involved in all stages of the atherosclerotic process. This review presents available evidence that identifies inflammation as a common pathophysiologic mechanism linking ED, the metabolic syndrome, and CAD. Furthermore the clinical implications in terms of ED diagnosis, risk determination, and therapy are discussed.

2. Endothelium, inflammation, and vasculogenic ED: pathophysiologic considerations

2.1. Pathophysiologic considerations of vasculogenic ED

Vasculogenic ED results from impairment of endothelial dependent or independent smooth muscle relaxation (functional vascular ED, initial stages), occlusion of the cavernosal arteries by atherosclerosis (structural vascular ED, late stages), or a combination of these [8,10–11]. Endothelial dysfunction is the key event in the pathophysiology of ED and, importantly, men with penile vascular

Table 1 – Studies evaluating subclinical inflammation and endothelial-prothrombotic activation in men with ED

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Age, yr, mean or range</th>
<th>IIEF-5, mean or %</th>
<th>Doppler PSV, cm/s, mean or %</th>
<th>Inflammatory and endothelial/prothrombotic markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiurlia et al. [6]</td>
<td>ED (n = 70)</td>
<td>51</td>
<td>12.7</td>
<td>27.5</td>
<td>hsCRP</td>
</tr>
<tr>
<td></td>
<td>Controls (n = 73)</td>
<td>50</td>
<td>22.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Billups et al. [27]</td>
<td>ED (n = 137)</td>
<td>20–64</td>
<td>MAI: 12</td>
<td>MAI*: 55.5%</td>
<td>hsCRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SAI: 10</td>
<td>SAI: 29.2%</td>
<td></td>
</tr>
<tr>
<td>Bocchio et al. [28]</td>
<td>ED no VRFs (n = 45)</td>
<td>45</td>
<td>22.1</td>
<td>NA</td>
<td>P-selectin, ICAM-1, VCAM-1, endothelin-1</td>
</tr>
<tr>
<td></td>
<td>ED with DM (n = 22)</td>
<td>53</td>
<td>13.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ED with HYP (n = 23)</td>
<td>55</td>
<td>10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls (n = 25)</td>
<td>46</td>
<td>15.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sullivan et al. [29]</td>
<td>ED (n = 96)</td>
<td>42–75</td>
<td>NA</td>
<td>NA</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td></td>
<td>Controls (n = 42)</td>
<td>42–68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esposito et al. [30]</td>
<td>MetS (n = 100)</td>
<td>38</td>
<td>&lt;21: 26.7%</td>
<td>NA</td>
<td>hsCRP</td>
</tr>
<tr>
<td></td>
<td>Controls (n = 50)</td>
<td>38</td>
<td>&lt;21: 13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giugliano et al. [31]</td>
<td>Obese ED (n = 40)</td>
<td>35–55</td>
<td>14.0</td>
<td>NA</td>
<td>hsCRP, IL-6, IL-8, IL-18</td>
</tr>
<tr>
<td></td>
<td>Obese no ED (n = 40)</td>
<td></td>
<td>23.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonobese (n = 50)</td>
<td></td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eaton et al. [32]</td>
<td>n = 988, mixed population with or without CAD</td>
<td>46–81</td>
<td>NA</td>
<td>NA</td>
<td>ICAM-1, VCAM-1, CRP, fibrinogen, IL-6, TNF-α</td>
</tr>
<tr>
<td>Vlachopoulos et al. [33]</td>
<td>No ED, no CAD (n = 32)</td>
<td>57</td>
<td>23</td>
<td>NA</td>
<td>hCRP, IL-1β, IL-6, TNF-α, fibrinogen, PAI-1, vWF (%)</td>
</tr>
<tr>
<td></td>
<td>ED, no CAD (n = 46)</td>
<td>59</td>
<td>13</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No ED, CAD (n = 25)</td>
<td>58</td>
<td>23</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ED-CAD (n = 38)</td>
<td>61</td>
<td>12</td>
<td>28.4</td>
<td></td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; DM = diabetes mellitus; ED = erectile dysfunction; hsCRP = high-sensitivity C-reactive protein; HYP = hypertension; IIEF-5 = International Index for Erectile Function (short version questionnaire, 5 questions); ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; MAI = mild arterial insufficiency; MetS = metabolic syndrome; NA = not applicable/available; PAI-1 = plasminogen activator inhibitor-1; PSV = peak systolic velocity; SAI = severe arterial insufficiency; tPA = tissue type plasminogen activator; TNF-α = tumor necrosis factor; VCAM-1 = vascular cell adhesion molecule-1; VRFs = vascular risk factors; VWF = von Willebrand factor.

* MAI: PSV = 25–35 cm/s; SAI: PSV < 25 cm/s.
dysfunction have endothelial dysfunction in other vascular beds as well [12]. Interestingly, the small diameter of the cavernosal arteries and the high content of endothelium on a per gram of tissue basis (compared with other organs) may make the penile vascular bed a sensitive indicator of systemic vascular disease [13].

2.2. Inflammation, endothelial dysfunction, and atherosclerosis

Normal vascular endothelium has anti-inflammatory properties; however, endothelial function is impaired in the presence of inflammatory conditions and increased oxidative stress [14]. Increased production of oxidative metabolic products is interrelated with activation of low-grade inflammatory mechanisms in the vascular wall [15]. We and others have shown that inflammatory stimuli impair arterial function both on an acute and chronic basis [16–19]. Furthermore, chronic low-grade inflammation and oxidative stress are closely related to atherosclerosis by contributing to all its stages, from the initial phase of increased endothelial permeability up to the formation of the mature atherosclerotic plaque and plaque rupture [20–22]. Increased levels of inflammatory markers have been documented in various settings of CAD, especially in acute coronary syndromes, bearing a strong association with clinical outcome. Although there is a lack of consensus on the implementation of blood level of inflammatory markers/mediators in everyday clinical practice, accumulating evidence suggests that some of these markers, especially C-reactive protein (CRP), may be of value as a clinical tool for assessment of cardiovascular risk or treatment efficacy [23–26].

2.3. Inflammation and ED

Several reports (Table 1) show that presence and severity of ED are associated with markers and mediators of subclinical inflammation and endothelial dysfunction. Plasma levels of high-sensitivity CRP (hsCRP) were significantly higher in patients with ED, compared with subjects without ED, matched for age and coronary risk score [6]. Furthermore, hsCRP levels have been associated with penile arterial disease severity assessed with penile Doppler ultrasonography in men with ED without clinically apparent cardiovascular disease [27]. Levels of intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) are also increased in men with ED but without cardiovascular risk factors or overt vascular damage [28]. In a preliminary study, fibrinogen levels were increased in ED patients compared to men with normal erectile function [29]. In addition, sporadic studies (discussed in more detail in Section 3) have linked ED with enhanced inflammatory state in men with metabolic syndrome.

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**Fig. 1** – (A) Spearman correlations of biochemical markers of inflammation with sexual performance as assessed by the Sexual Health Inventory for Men (SHIM) score in the whole study population. (B) Charts showing the diagnostic performance of fibrinogen and interleukin 6 for erectile dysfunction at cut-off values associated with 95% sensitivity. Adapted with permission from Vlachopoulos C, et al. [33].
syndrome or obesity [30,31]. Furthermore, although a recent retrospective study did not find any association between the level of inflammatory activation and self-reported ED [32], we recently showed that sexual performance assessed by the International Index of Erectile Function 5 (IIEF-5) score correlates inversely with the circulating levels of endothelial prothrombotic and inflammatory parameters such as fibrinogen, von Willebrand factor, and interleukin (IL) 1β and IL-6 (Fig. 1) [33]. It should be stressed, however, that the aforementioned cross-sectional, observational studies, despite being very insightful, do not necessarily prove causality.

The inverse association between erectile performance and oxidative stress has been highlighted recently [34,35]. Increased production of reactive oxygen species (such as superoxide and peroxynitrite) in subjects with cardiovascular risk factors decrease bioavailability of nitric oxide (NO) and may lead to ED.

Although the penis vasculature may be the target of a widespread inflammation generated elsewhere, it is interesting to note that this organ may itself actively participate in the whole process. The human corpus cavernosum is an angiotensin II-producing paracrine system [36] and a deletion polymorphism in the gene encoding angiotensin-converting enzyme (ACE; DD genotype) has been reported to be more common in men with a diagnosis of organic ED [37]. Angiotensin II triggers

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Age, yr</th>
<th>MetS prevalence, %</th>
<th>ED evaluation</th>
<th>MetS criteria*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito et al. [30]</td>
<td>150</td>
<td>38 ± 3</td>
<td>66%</td>
<td>IIEF-5</td>
<td>NCEP-ATPIII</td>
<td>ED prevalence increases as the number of components of the MetS increases.</td>
</tr>
<tr>
<td>Bansal et al. [40]</td>
<td>154</td>
<td>53.5 ± 10</td>
<td>43%</td>
<td>IIEF-5</td>
<td>NCEP-ATPIII</td>
<td>Men with ED have a high incidence of MetS.</td>
</tr>
<tr>
<td>Grover et al. [1]</td>
<td>3921</td>
<td>40–88</td>
<td>37.9 % among ED patients</td>
<td>IIEF-EFD</td>
<td>NCEP-ATPIII</td>
<td>ED was independently associated with MetS (OR, 1.45; 95%CI, 1.24–1.69; p &lt; 0.001).</td>
</tr>
<tr>
<td>Corona et al. [41]</td>
<td>803</td>
<td>53.6 ± 12</td>
<td>29.4%</td>
<td>SIEDY, penile Doppler ultrasound</td>
<td>NCEP-ATPIII</td>
<td>MetS is associated with a more severe ED.</td>
</tr>
<tr>
<td>Demir et al. [42]</td>
<td>268</td>
<td>54 ± 9</td>
<td>33%</td>
<td>IIEF-EFD</td>
<td>NCEP-ATPIII</td>
<td>MetS is significantly associated with ED.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ED severity increases as the number of components of the MetS increases.</td>
</tr>
<tr>
<td>Kupelian et al. [43]</td>
<td>928</td>
<td>40–70</td>
<td>no MetS at baseline</td>
<td>Self-administered questionnaire</td>
<td>NCEP-ATPIII</td>
<td>ED is predictive of MetS only in men with BMI &lt; 25 kg/m².</td>
</tr>
<tr>
<td>Bal et al. [44]</td>
<td>393</td>
<td>56 ± 8</td>
<td>40%</td>
<td>IIEF-EFD</td>
<td>NCEP-ATPIII</td>
<td>MetS is strongly associated with ED.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting blood glucose levels, hypertension, and waist circumference are the most significant risk factors predicting the risk of ED.</td>
</tr>
<tr>
<td>Heidler et al. [3]</td>
<td>2371</td>
<td>46 ± 10</td>
<td>33.8%</td>
<td>IIEF-5</td>
<td>NCEP-ATPIII</td>
<td>The MetS and an increased waist-to-hip ratio are independently associated with a decreased IIEF score. The MetS criteria seem to be a better predictor of impaired penile blood flow than IDF ones.</td>
</tr>
<tr>
<td>Corona et al. [45]</td>
<td>1086</td>
<td>52 ± 13</td>
<td>32.9%</td>
<td>Penile Doppler ultrasound</td>
<td>NCEP-ATPIII-IDF</td>
<td>In patients with ED, NCEP-ATPIII criteria seem to be a better predictor of impaired penile blood flow than IDF ones.</td>
</tr>
</tbody>
</table>

BMI = body-mass index; CI = confidence interval; ED = erectile dysfunction; IIEF-5 = International Index for Erectile Function (short version questionnaire, 5 questions); IIEF-EFD = International Index for Erectile Function–Erectile Function Domain; IDF = International Diabetes Federation; MetS = metabolic syndrome; NCEP-ATPIII = National Cholesterol Education Program–Third Adult Treatment; OR = odds ratio; SIEDY = Structured Interview on Erectile Dysfunction.

* The NCEP-ATPIII definition of MetS was defined as the presence of three or more of the following five factors: central obesity (waist circumference > 102 cm), elevated triglycerides (≥ 1.7 mmol/l or 150 mg/dl), elevated blood pressure (≥ 130/85 mm Hg), elevated fasting glucose (≥ 6.1 mmol/l or 110 mg/dl), and reduced high-density lipoprotein (HDL) cholesterol (≤ 1.03 mmol/l or 40 mg/dl). The IDF definition of MetS consists of the same five factors as the NCEP-ATPIII definition, but with different values for the classification of increased waist circumference (≥ 94 cm) and fasting glucose (≥ 5.5 mmol/l or 100 mg/dl).
vascular inflammation by inducing oxidative stress and regulating the release of inflammatory mediators, such as IL-6\(^{[38]}\), by increasing the expression of adhesion molecules and by enhancing the penetration of monocytes/macrophages into the vessel wall\(^{[39]}\).

3. Metabolic syndrome, ED, and low-grade systemic Inflammation

3.1. Metabolic syndrome and ED

Central obesity together with hypertension, dyslipidemia, and insulin resistance defines the metabolic syndrome. The above-mentioned risk factors appear to carry a threat to the penile endothelium and the smooth muscle tissue leading to functional and structural changes in the cavernous arteries. Indeed, clinical and epidemiologic studies (Table 2) support an association between metabolic syndrome and ED\(^{[1–3,30,40–45]}\). Metabolic syndrome and increased waist-to-hip ratio have been associated with a higher proportion of moderate to severe ED in men older than 50 yr\(^{[3]}\). Conversely, ED may be predictive of metabolic syndrome presence in men with a body mass index (BMI) of <25 kg/m\(^2\)\(^{[43]}\). This interesting finding suggests that ED may be a warning sign in men otherwise considered at low cardiovascular risk.

3.2. Metabolic syndrome and inflammation

Chronic inflammation appears to be involved in the pathogenesis of the metabolic syndrome (Fig. 2).

Stimuli such as overnutrition and physical inactivity may result in cytokine overproduction and eventually may lead to insulin resistance in genetically or metabolically predisposed individuals. Alternatively, resistance to the anti-inflammatory actions of insulin may result in enhanced circulating levels of proinflammatory cytokines, which, in turn, may lead in persistent low-grade inflammation. A general enhanced adipose tissue-derived cytokine expression may be another plausible mechanism for the inflammation/metabolic syndrome relationship\(^{[46–48]}\). In line with these, recent data have revealed that the plasma concentration of inflammatory markers/mediators, such as tumor necrosis factor \(\alpha\), (TNF-\(\alpha\)), IL-6, hsCRP, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) levels are increased in the insulin-resistant states of obesity and type 2 diabetes\(^{[46]}\).

3.3. Metabolic syndrome-inflammation-ED

Studies have linked the metabolic syndrome and ED with inflammation. Patients with metabolic syndrome had an increased prevalence of ED, reduced endothelial function score, and higher circulating concentrations of hsCRP compared with men without metabolic disorders\(^{[30]}\). Interestingly, as the number of the components of metabolic syndrome increased, the inflammatory-endothelial activation was more severe and the prevalence of ED was higher. In another study, circulating hsCRP levels were significantly higher in obese men with ED as compared with obese men without ED\(^{[31]}\) and erectile function score was negatively associated with BMI, waist-to-hip ratio, and hsCRP. However, whether ED is accompanied by an incremental inflammatory and prothrombotic activation on top of metabolic syndrome remains to be elucidated.

4. CAD, ED, and low-grade systemic inflammation

4.1. CAD and ED

Vasculogenic changes in the penile vascular bed mirror those in the coronary arteries and ED is closely related to CAD at the clinical level. Among patients with established CAD, ED prevalence is reported to range from 33% to 75%\(^{[49–52]}\). Recently, Montorsi et al reported that ED rate differs significantly in patients with established CAD according to clinical presentation of CAD and atherosclerosis burden. It is low in acute coronary symptoms and single-vessel disease and it is high in chronic and...
multivessel CAD (Fig. 3). Furthermore, ED severity, but not ED prevalence, was also correlated with coronary plaque burden and number of diseased coronary arteries [9].

Addressing in a converse way the association between CAD and ED, it is important to recognize how earlier the clinical manifestation of ED precedes the clinical manifestation of CAD. According to the “artery size” hypothesis, the smaller penile arteries suffer obstruction from plaque burden earlier than the larger coronary arteries; hence, ED may be symptomatic before CAD becomes clinically evident [8]. In men with both ED and CAD, erectile function abnormalities have been reported to precede CAD manifestation by a mean time interval of almost 3 yr [7,9,50]. This relatively long phase lag offers important potential in estimating and, ultimately, reducing cardiovascular risk in men with ED. However, it should be stressed that the penis is not always the most susceptible organ to inflammatory and atherosclerotic changes. Accordingly, although ED frequently precedes the onset of CAD, a considerable proportion of patients have CAD without concomitant ED, proving that the clinical course of atherosclerosis is multifaceted and not fully predictable.

An important issue that deserves specific attention is whether patients who present with ED have concomitant subclinical CAD. Several studies have tried to unravel this association [53–55]. Highlighting some of these, the prevalence and extent of coronary atherosclerosis as assessed by coronary artery calcification was significantly higher among patients with ED and could not be predicted by the presence of traditional risk factors for cardiovascular disease [6]. Importantly, a prospective angiographic study showed that almost one in five men presented with erectile function abnormalities of vascular origin had angiographically documented silent CAD [7]. This is a substantially higher prevalence than the 4% CAD prevalence that was found in a previous study in the general population [56]. Findings such as these underscore the need to identify those ED patients needing further investigation for silent CAD.

4.2. Inflammation, CAD, and ED

Recently, the association between low-grade inflammation and altered endothelial-prothrombotic state and ED was evaluated in men with and without CAD through a thorough approach that integrated a wide spectrum of circulating markers and mediators [33]. ED was related to significantly increased circulating levels of such variables, both in patients with or without CAD, suggesting that ED adds an incremental inflammatory and endothelial-prothrombotic activation on top of CAD. Interestingly enough, no significant difference was observed for many inflammatory and endothelial-prothrombotic substances between men with ED only and men with CAD but normal erectile function. Although an extrapolation, this could be interpreted as equivalence between ED and CAD in terms of endothelial or inflammatory activation, and it indicates that ED may comprise an alternative phenotype in patients with generalized vascular disease.
5. Evaluation of inflammatory state in patients with ED: clinical implications

Apart from elucidation of pathophysiologic mechanisms, evaluation of inflammatory status has the potential to be useful in the clinical setting. In particular, it can be used in diagnosing patients with possible ED, assessing patient risk, and monitoring therapy of patients with ED.

5.1. Diagnosis or exclusion of ED

Biomarkers assist in the diagnosis of diseases based on their diagnostic performance. Clinicians cannot rely on any particular biochemical marker to diagnose (“rule in”) ED [33]. However, in diseases like ED there is a need for biomarkers with a high negative predictive value (ability to “rule out” the disease in patients with suspected ED based on high sensitivity, that is, on low false-negative results). This is because (1) ED carries important independent risk [4,5] and (2) current treatment with phosphodiesterase type 5 (PDE5) inhibitors is effective, safe, and, importantly, evidence suggests that it can, in addition, improve overall cardiovascular performance [57–60]. In other words, it is imperative that a biomarker should help not “missing” cases of ED because the overall benefit from treating these patients with a proven safe treatment is great. In search of such inflammatory biomarkers, we recently showed that cut-off values of 225 mg/dl for fibrinogen and 1.24 pg/ml for IL-6 were associated with a negative predictive value (ability to “rule out” ED) of 85.2% and 81.0%, respectively. When these two cut-off limits were combined, the negative predictive value was 91.7%, meaning that subjects who had fibrinogen and IL-6 levels below the aforementioned cut-off levels had a 0.917 probability of being free of ED [33]. Undoubtedly, it would be very interesting to further examine whether combining other proinflammatory markers may increase the negative predictive value.

5.2. Assessment of patient risk: implications for prognosis

An important feature in the clinical course of ED is that it often precedes clinically evident CAD by a considerable amount of time [7,9,50]. Thus, identification of patients at high risk for future cardiac events is of paramount importance because adequate time is given to intervene.

Inflammatory biochemical variables are predictive of future cardiovascular outcomes [25,61,62]. Thus, the incremental inflammatory activation that ED adds on top of CAD and the “inflammatory equivalence” between ED and CAD [33] suggest that patients with increased levels of such variables may have an associated independently increased risk of cardiovascular events attributed to ED.

Inflammation contributes both to an increase of the atherosclerotic burden (chronic CAD) but also to vulnerable plaque destabilization and rupture (acute coronary syndromes). The latter is particularly important because, first, it has an unpredictable and emergent nature and, second, most of acute coronary events are caused by vulnerable plaques that cause mild rather than critical stenosis [63]. Thus, ED diagnosis undoubtedly calls for prospective follow-up of patients for identification of development of flow-limiting coronary lesions according to the “artery-size hypothesis” of Montorsi et al [8]. On the other hand, because the absence of severe, obstructive coronary atherosclerotic lesions does not preclude the occurrence of acute coronary events in patients with ED and no clinical evidence of CAD, measurement of inflammatory markers may be particularly important given the role of inflammation for the rupture of unstable plaques (Fig. 2).

Although some inflammatory markers, such as fibrinogen [64], may be more relevant to the progression of atherosclerotic burden, other markers may be more important for plaque instability. Indeed, hsCRP may serve as an example [23,24]. In contrast to the unequivocal findings on the relationship between hsCRP and incident cardiovascular events, epidemiologic studies of general populations have found inconsistent associations between hsCRP and measures of subclinical atherosclerosis such as carotid intimal-medial thickness (IMT) [65,66]. In this context, increased CRP levels may primarily reflect an increased tendency for plaque rupture rather than a high atherosclerotic burden in ED patients [26].

Accordingly, evaluation of a broad profile of inflammatory markers and mediators can target different stages of the atherosclerotic, inflammatory, and thrombotic cascades. Given the complementary and independent prognostic value of various inflammatory markers, a “multimarker” approach in men with ED may be an effective strategy to improve prediction of cardiovascular risk beyond the use of traditional risk factors in daily clinical practice.

5.3. Treatment

Treatment for ED includes modification of risk factors and administration of PDE5 inhibitors, whereas other non-ED drugs such as statins have
also a promising potential. Although not proven at this stage, part of the beneficial effect of these treatment strategies may be mediated through a beneficial modification of inflammatory state.

5.3.1. Risk factor and lifestyle modifications

In an intervention study of men with ED and metabolic syndrome, the Mediterranean-style diet led to an improvement of erectile function score (IIEF-5) after 2 yr; impressively, about one third of men of the intervention group regained a normal erectile function. Endothelial function score and inflammatory markers (hsCRP) significantly improved in the intervention group, but not in the control group [67]. Furthermore, in a single-blind trial of obese men (BMI ≥ 30) with ED but without diabetes, hypertension, or hyperlipidemia, reduction of total body weight by ≥10% and increase of level of physical activity were associated with an improvement in the IIEF-5 score and reduction in serum concentrations of IL-6 and hsCRP after 2 yr [68].

5.3.2. PDE5 inhibitors

Evidence indicates that PDE5 inhibitors have a beneficial effect on inflammatory activation. Although exact mechanisms are not fully known, the basis for these anti-inflammatory effects is the increased activity of the NO-cyclic guanosine monophosphate axis (NO-cGMP). Through the up-regulation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase cytokines not only increase formation of superoxide but they also up-regulate the expression of PDE5. PDE5 inhibitors antagonize these inflammatory effects by enhancing the NO-cGMP axis, which, apart from augmenting smooth muscle cell relaxation, also inhibits NADPH-oxidase expression/activity [69]. We and others have shown that sildenafil has both acute and chronic beneficial effects on arterial function in men with ED [57–59,70]. Given the unfavorable effect of inflammation on arterial function [17], this effect could be partly attributed to an anti-inflammatory action of sildenafil and, indeed, this is supported by preliminary data from our laboratory (C. Vlachopoulos et al, unpubl. data). Moreover, a 12-wk antioxidant treatment (propionyl L-carnitine) plus sildenafil reduced monocyte activation and markers of endothelial (ICAM-1, P-selectin) and penile vascular (end-diastolic velocity [EDV]) damage in patients with diabetic ED [71]. In a recent study, a 3-wk treatment with tadalafil was accompanied by a favorable effect on endothelium-dependent vasodilatation of cavernous arteries in men with ED [72]. This was accompanied with a favorable effect on markers of endothelial function and inflammation including VCAM and ICAM, endothelin-1, and hsCRP as well as on insulin. Tadalafil also significantly decreased hypoxia-induced up-regulation of TNF-α and IL-1ß expression in pulmonary arteries [73].

5.3.3. Other non-ED drugs

Statins exert beneficial effects independent of cholesterol-lowering, the so-called pleiotropic effects that involve improvement of endothelial function, decrease of inflammation and thrombogenesis, and stabilization of atherosclerotic plaque. Recent studies investigating the effects of statins on erectile function in men with ED demonstrate that the favorable effect of these drugs can be at least in part attributed to their action on the endothelium, possibly through their anti-inflammatory properties [74].

A 6-mo administration of an ACE inhibitor (quinapril) in men with advanced atherosclerotic ED, demonstrated remarkable beneficial effects on cavernosal perfusion, sexual activity, and erectile function [75]. Angiotensin II is both an important modulator of erectile function and proinflammatory agent [36,37]. Accordingly, renin-angiotensin-aldosterone blockers appear to favorably affect erectile function through multiple modes of action.

6. Conclusions

Recent findings have pointed toward an important role of low-grade inflammation in the pathogenesis of vasculogenic ED in various patient subgroups. ED appears to be a “CAD equivalent” in terms of inflammatory activation and endothelial-prothrombotic activation and confers an incremental unfavorable impact when combined with the latter disorder. Subclinical inflammation may comprise a common pathophysiologic denominator of metabolic syndrome, ED, and CAD; however, because complex interrelationships exist, it is difficult to define exactly the causal pathways in these disorders. Evaluation of inflammatory activation in the clinical setting may improve the diagnostic approach of patients with suspected ED and may identify patients at higher risk for cardiovascular events. Finally, it appears that lifestyle and risk factor modification and pharmacologic therapy (both PDE5 inhibitors and non–ED-targeting drugs) confer additional benefit both in terms of ED treatment and overall cardiovascular risk, and this benefit is perhaps related, at least partly, to anti-inflammatory effects.
Conflicts of interest

The authors have nothing to disclose.

References


