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Basic Science Evidence for the Link Between Erectile Dysfunction and Cardiometabolic Dysfunction

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Abstract

Introduction—Although clinical evidence supports an association between cardiovascular/metabolic diseases (CVMD) and erectile dysfunction (ED), scientific evidence for this link is incompletely elucidated.

Aim—This study aims to provide scientific evidence for the link between CVMD and ED.

Methods—In this White Paper, the Basic Science Committee of the Sexual Medicine Society of North America assessed the current literature on basic scientific support for a mechanistic link between ED and CVMD, and deficiencies in this regard with a critical assessment of current preclinical models of disease.

Results—A link exists between ED and CVMD on several grounds: the endothelium (endothelium-derived nitric oxide and oxidative stress imbalance); smooth muscle (SM) (SM abundance and altered molecular regulation of SM contractility); autonomic innervation (autonomic neuropathy and decreased neuronal-derived nitric oxide); hormones (impaired testosterone release and actions); and metabolics (hyperlipidemia, advanced glycation end product formation).

Conclusion—Basic science evidence supports the link between ED and CVMD. The Committee also highlighted gaps in knowledge and provided recommendations for guiding further scientific study defining this risk relationship. This endeavor serves to develop novel strategic directions for therapeutic interventions.

Keywords

Endothelium; Smooth Muscle; Autonomic Regulation; Hormones; Metabolics

Introduction: Arthur L. Burnett, Trinity J. Bivalacqua

Because erectile dysfunction as a term is so widely mentioned nowadays within both the medical professional and lay public communities, many understand its basic meaning and reference to sexual dysfunction. However, its clinical implications are far more extensive and likely less well understood. The entity, otherwise commonly referred to as “ED,” is accurately defined as the inability to attain and maintain a satisfactory erection of the penis to permit sexual intercourse sufficiently [1], which therefore serves effectively to establish the boundaries of the sexual dysfunction among a host of male sexual disorders. It is fair

also to comprehend the term as a descriptive symptom, in acknowledgment that it portrays erection difficulty or inability without specific attribution to a medical disease. However, this sexual dysfunction is indisputably associated with underlying adverse health conditions and risk factors [2–4], and clinical evaluation is used to establish the apparent clinical association [5,6]. Current biomedical advances in sexual medicine affirm its real pathophysiologic basis and support its strong links with clinical health and disease [7,8]. Moreover, beyond its multiple associations with health co-morbidities, ED appears also to carry long-term health risks and adversely impact survival [9–11].

Diverse comorbidity links with ED include both well-known disease states such as diabetes mellitus (DM), hypertension, and peripheral vascular disease [2–4] but also newly described associations such as epilepsy, urinary calculi, and periodontitis [12–14]. Cardiovascular/metabolic diseases (CVMDs) are most strongly linked with ED, with numerous studies having demonstrated these relationships [15–18]. Reports of an ED and CVMD link date back as much as 20 years with particular reference to the landmark publication of the Massachusetts Male Aging Study, which originally showed a higher probability of ED in men with cardiovascular disease (CVD), hypertension, dyslipidemia, and DM among other co-morbidities and risk factors [19].

Other studies have substantiated these findings and further described features of the risk relationship. Evidence in support of a temporal relationship whereby ED precedes manifestations of CVD was early provided by Montorsi et al. [15] whose evaluation of 300 consecutive patients with acute chest pain and angiographically confirmed coronary artery disease (CAD) revealed a 49% ED prevalence rate and documented that ED preceded CAD symptoms in 67% of patients. The placebo arm of the Prostate Cancer Prevention Trial similarly found that ED signals the risk of future cardiovascular events, comparable to that of current cigarette smoking or a family history of myocardial infarction, such that men with ED were 45% more likely than men without ED to experience a cardiac event after 5 years of follow-up [20]. The severity of ED also characterizes the relationship, based on work by Pohnholzer et al. who found that moderate to severe ED (IIEF5 5–16), but not mild ED, was associated with increased risk for CAD or cerebrovascular disease within 10 years [21]. Others have also correlated the severity of ED with the extent of atherosclerotic CAD [22,23]. The added risk variable of associated metabolic disease such as DM in linking ED and CAD was shown with a heightened probability of CAD and CVD events in patients with type 2 DM (T2DM) in several studies [24–27]. It is acknowledged that not all investigators evaluating a possible link between ED and CVD have supported a risk relationship [28,29].

Recent meta-analyses of longitudinal studies have further provided relative risk ratios for assorted cardiovascular conditions and related mortality for men with ED [30–33]. A meta-analysis of seven prospective cohort studies determined adjusted relative risks for ED subjects compared with healthy subject to be 1.47 for CVD events overall and 1.23 for increased all-cause mortality [30]. In a meta-analysis comprising 12 cohort studies, overall combined relative risks for men with ED compared with the reference group without ED were found to be 1.48 for CVD, 1.46 for coronary heart disease, 1.35 for stroke, and 1.19 for all-cause mortality [31]. In another meta-analysis comprising 14 studies, documented relative risks were 1.44 for cardiovascular mortality, 1.19 for myocardial infarction, 1.62 for

cerebrovascular events, and 1.25 for all-cause mortality for men with ED relative to those without ED [32]. In a quite large cohort study representing 95,038 men without previous CVD, adjusted relative risks for men with severe ED compared to those without ED were 1.60 for ischemic heart disease, 8.00 for heart failure, 1.92 for peripheral vascular disease, 1.26 for “other” CVD, 1.35 for all CVD combined, and 1.93 for all-cause mortality [33].

In view of the preponderance of clinical epidemiologic evidence supporting the link between ED and CVMD, several consensus organizations have promulgated a view that recognizing ED offers clinical utility beyond ED treatment [34–36]. This view contends that the presence of ED offers a clinical opportunity to manage cardiovascular and metabolic health applying the premise that ED represents a valid barometer or biomarker of health status and is moreover a harbinger of subsequent CVMD. The Princeton Consensus Conferences, a multidisciplinary forum convened on three occasions since the early 2000s, have pronounced that all men with ED, even in the absence of manifesting cardiac symptoms, should be regarded as possessing potential cardiovascular health risks [37–39].

Amid the advancing clinical practice of co-managing ED and CVMD, it has remained necessary to account for the risk relationship on mechanistic grounds. Some thought leaders have proposed such concepts as “endothelial dysfunction” as a possible explanation for the risk relationship suggesting that this pathomechanism at the penile vascular level constitutes a universal vascular derangement (which may coexist with or in fact precede occurrences of vascular disease elsewhere) [40,41]. In line with this dogma, maxims such as “ED = ED,” translated as “erectile dysfunction equals endothelial dysfunction,” have been widely accepted in medical parlance and advanced in the literature. However, it is entirely possible and even more plausible that multiple pathomechanisms linking ED and CVMD are in play beyond simply dysfunctional endothelium. The vascular abnormality associated with ED, for instance, may involve dysfunctional corporal vascular and trabecular smooth muscle (SM), and this dysfunction may well significantly underlie clinical descriptions of corporal veno-occlusive dysfunction [42,43]. Besides the vascular component altogether, other functional systems ranging from aberrant nervous (e.g., autonomic neurotransmission) to hormonal (e.g., testosterone release and actions) to metabolic (e.g., hyperlipidemia, advanced glycation end product formation) are likely involved and should be considered. Scientific study is needed to address the validity of the supposed link between ED and CVMD, broadly evaluating the roles of alternative functional systems and their molecular mechanisms.

This White Paper was conceived in recognition that the scientific evidence linking ED and CVMD is at present incompletely elucidated. The Basic Science Committee of the Sexual Medicine Society of North America (SMSNA) was commissioned in 2012 to conduct a comprehensive literature review of this subject from a basic scientific perspective, evaluating the evidence basis for a mechanistic link between ED and CVMD. The Committee was assigned with assessing the current scientific levels of support for a mechanistic link while also identifying deficiencies in this regard with a critical assessment of current pre-clinical models of disease. In doing so, the Committee would determine whether the position of a link is justified and on what basis this is so. The further objective then for the Committee was to provide recommendations for guiding further scientific study defining the risk relationship, with the additional potential to describe novel strategic directions for

therapeutic interventions. Accordingly, the review is structured as sections representing distinct functional systems that are relevant for erection physiology. A summary and synthesis comprise a concluding section.

Endothelium: Biljana Musicki, Christopher J. Wingard

Introduction

In this section, we review and critically evaluate the literature on endothelium which supports, or not, ED being the harbinger of CVMD. We highlight findings from in vivo and in vitro animal studies and molecular pathways common to ED and CVMD.

The penis is a highly vascularized organ, and penile erection is, in large part, a neurovascular event which requires functional endothelium in addition to SM and intact neural input. The endothelium produces several vasodilatory factors, including nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor, as well as endothelium-derived thromboxane A₂, endothelin-1, and superoxide anion promoting vasoconstriction. Any disruption of normal endothelial cell function may affect penile blood flow and compromise the erection.

Vascular disorders are a significant basis for the development of ED [43]. Endothelial dysfunction, which accompanies vascular disorders, can be defined as either decreased responsiveness to vasodilators or increased sensitivity to vaso-constrictors [44]. In a broader sense, endothelial dysfunction also encompasses altered anticoagulation and anti-inflammatory activities, impaired modulation of vascular growth, and dysregulation of vascular remodeling. Major cardiometabolic risk factors, including DM, hypertension, hypercholesterolemia, obesity, sedentary life style, smoking, and aging, are all associated with endothelial dysfunction.

Endothelial dysfunction can occur in any vascular bed but is considered a common denominator when both ED and peripheral vascular disease are present, providing a plausible link between ED and CVMD. Impaired NO signaling, oxidative stress, and structural abnormalities are key mechanisms underlying penile and systemic vasculopathies.

Temporal Relationship Between ED and Endothelial Dysfunction in the Systemic Vasculature

The temporal relationship between ED and endothelial dysfunction of the systemic vasculature in the basic science literature is conflicting. Several studies evaluated endothelium-dependent vasorelaxation in the corpora cavernosa and systemic blood vessels in animal models of vascular diseases and reported parallel impairment in endothelial function. In a mouse model of type 1 DM (T1DM), endothelium-dependent vasorelaxation was decreased in both the penis and aorta at 4 and 6 weeks after DM induction [45,46] presumably through mechanisms involving protein kinase C (PKC) β activation and impairment in cholesterol biosynthesis. Investigations using rat models of T1DM found that endothelium-dependent vasorelaxation was decreased in the corpus cavernosum and aorta 8 weeks after DM induction and was associated with increased oxidative stress, protein

expression of caveolin-1, a proinflammatory state, activation of protein tyrosine kinase, and inhibition of peroxisome proliferator-activated receptor- γ [47–52].

Dietary manipulations have also been useful in examining the connection between systemic and penile endothelial function in light of their cardiometabolic challenges. In a rat model of high fructose feeding for 8 weeks, depressed endothelium-dependent vasorelaxation of the aorta and corpus cavernosum was due to the disruption of peroxisome proliferator-activated receptor- γ signaling and increased caveolin-1 expression [49]. In a mouse model of hypercholesterolemia (apolipoprotein E knockout mice on high fat diet for 7–8 weeks), endothelial function was impaired, along with increased production of reactive oxygen species and activation of the renin-angiotensin system, in both the aorta and corpus cavernosum [53–55]. Six weeks of high fat feeding in a rabbit model reduced endothelium-dependent vasorelaxation of the thoracic aorta, renal artery, and corpus cavernosum [56]. The underlying mechanisms of endothelial dysfunction suggested a common denominator of reactive oxygen species production, but the precise mechanism of endothelial dysfunction, and specifically any interaction between regulatory elements like caveolin-1 and endothelial NO synthase (eNOS) or the mechanism of PKC activation and its downstream signaling in the penis were not evaluated.

In contrast to those results, several recent reports provided evidence for a vulnerability of the penile vasculature that is not present in other systemic vasculatures. These studies report endothelial dysfunction in the penile vascular bed occurring prior to those of the aorta or coronary and mesenteric arteries. In obese Zucker rats (OZR), a genetic model of insulin resistance, the impairment of endothelium-dependent relaxation was apparent in the dorsal penile artery but not in the coronary artery at >17 weeks of age [57], while ED developed between 16–20 weeks of age [58], and impaired coronary vasodilator response to acetylcholine occurred after 28 weeks of age [59]. In Sprague Dawley rats fed a high cholesterol diet, erectile function was impaired after 2 weeks, while endothelium-dependent relaxation of the thoracic aorta was maintained [60]. In other studies using a Western diet (consisting of high fat/high sugar), decreased erectile function was noted after 8 weeks, while endothelium-dependent relaxation of the coronary artery was impaired after 12 weeks [61]. Additionally, Park et al. [62] found that a cholesterol diet alone for 6 weeks in Sprague Dawley rats resulted in mild vasculogenic ED without any significant pelvic arterial pathology. Only after adding intermittent inhibition of NO generation did they observe atherosclerotic pathologies in segments of pelvic arteries progressing from distal to proximal regions. While in a mildly aged rat model and a model of chronic kidney disease endothelium-dependent relaxation of the pudendal artery and erectile response were impaired, endothelial function of the mesenteric and coronary arteries remained intact [63,64].

A series of separate studies, using similar animal models, reported a time-dependent appearance of endothelial dysfunction, which occurred first in the penile vasculature and later in other peripheral vascular beds. For example, in a rat model of high-fat diet/low-dose streptozotocin-induced T2DM, ED was obvious as early as 4 weeks of DM [65], while decreased endothelium-dependent vasorelaxation in the posterior ciliary artery [66], epineurial arterioles [67], and the aorta [68] was apparent 12–16 weeks after DM induction.

Collectively, these basic science studies suggest that the development of endothelial dysfunction in different vascular beds is time dependent and that endothelial dysfunction likely occurs in the penis prior to its onset in other vascular beds.

Role for Endothelial Cells in the Link Between ED and CVMD

The artery size hypothesis has been invoked to explain why ED precedes CVD [69]. According to this hypothesis, because of the small diameter of cavernosal and helicine arteries (<1–2 mm), erectile tissue is prone to early manifestation of endothelial dysfunction and atherosclerosis: Smaller diameter makes penile arteries more prone to not sustain sufficient blood flow for penile erection even with minimal narrowing of the lumen, whereas the larger vessels (i.e., coronary arteries) can accommodate more narrowing and plaque deposition without large changes in blood flow; therefore, ED becomes evident earlier than CVD. The size hypothesis assumes that the endothelium is the same throughout the arterial tree, and vascular disease affects all vascular beds equally.

However, cavernosal endothelial cells exhibit some unique characteristics. Compared with human coronary artery and umbilical vein endothelial cells, human cavernosal endothelial cells express high levels of mRNA for collagen types I, III, IV, and VI, possibly relevant to sinusoidal space distensibility and the integrity of the venoocclusive mechanism requirement for rigid erection [70]. Components of endothelial cell junction complexes also differ at the gene and protein levels between cavernosal endothelial cells and endothelial cells from other vascular beds. These junctional complexes control a variety of cellular processes, including adhesion, paracellular transport, growth and apoptosis, and signaling events [71]. The tissue specificity of these components indicates that they may provide selective cell–cell recognition and/or specific functional properties. Wessells et al. [70] found greater expression levels of cadherin 2 (a cell–cell adhesion molecule of adherens junction) and claudin-11 (a tight junction protein) in cavernosal endothelial cells compared with that of coronary artery or umbilical vein endothelial cells and suggested they reflect a requirement for junctional and barrier integrity associated with high intracavernosal pressure during erection. Alterations in the integrity of the corpora cavernosa endothelial cell–cell junction, but not from those of the coronary and femoral arteries, have been reported in a T1DM mouse model [72]. The greater vascular permeability in the corpora cavernosa is correlated with sparse distribution of platelet endothelial cell adhesion molecule-1 and occludin, possibly contributing to a greater vulnerability of endothelial cell communication in the penis [72]. These findings are in line with the known structural and functional heterogeneity of the endothelium between vascular beds, implying that the endothelium is morphologically and functionally adapted to meet the unique demands of the underlying tissue [73].

In addition to differences in endothelial cell junctions, several other mechanisms have been described which may explain why ED precedes endothelial dysfunction in other vascular beds. In rats on Western diet for 12 weeks, activation of BH₄-dependent eNOS dysfunction (presumed “uncoupling”) was unique to the penile vasculature and did not affect the coronary artery [74]. In Zucker rats, structural deterioration (the internal diameter and the wall-to-lumen ratio) of the dorsal penile artery was apparent at a time (17–18 weeks of age) when no structural changes were present in the coronary artery [57]. Similarly, aging exerted

a greater pathological vascular remodeling of the pudendal arteries compared with that of the aorta and renal arteries [63].

Conclusions

Common risk factors (such as DM, hypertension, etc.) affect the endothelium of vascular beds, providing the common link between ED and CVMD. However, mechanisms of endothelial dysfunction in the penile circulation, which contribute to ED, may differ from that of other vascular beds (Figure 1). Basic science data suggest that there is a temporal relationship between penile and systemic vascular beds, supporting clinical observations that ED precedes CVMD. Continuing basic science research is needed to critically evaluate mechanisms unique to endothelium which underlie the apparent temporal relationship between penile and systemic vascular beds in response to cardiometabolic risk factors.

Smooth Muscle: Michael E. DiSanto

Introduction

Although it has been suggested that endothelial dysfunction is a primary contributor to the development of ED, a strong case has also been made for a major role of SM dysfunction [75–78]. The stimulus for erection derives from the brain via the central nervous system, triggering the release of NO from both neuronal and endothelial cells via neuronal nitric oxide synthase (nNOS) and eNOS. Central to the molecular basis of erection is the regulated contraction and relaxation of corpus cavernosum SM [43]. If there is an alteration in SM abundance or in the molecular composition/regulation of SM, irrespective of NO release, corpus cavernosum SM relaxation needed for proper erection may not occur [79–81].

Over the last 2 decades, an association between ED and CVMD has been suggested, and researchers have hypothesized a link exists between the two conditions. The objective of this section is to summarize and evaluate the strength of the evidence for the proposed link between ED and CVD from the perspective of altered SM and to propose the types of studies needed to more clearly define the molecular mechanisms mediating this link.

Role for SM in the Link Between ED and CAD

Using a rat model of T1DM, Elçio lu et al. reported that after 8 weeks of streptozotocin-induced DM, the maximum contraction of the corpus cavernosum SM to phenylephrine was reduced by about 50%, whereas the maximum contraction of the aorta was reduced less [50]. Similarly, the EC₅₀ was reduced by about 10-fold for the corpus cavernosum SM but only by about threefold for the aorta. This study confirmed an earlier study by the same group [49] in which they examined a fructose-induced T2DM group, which demonstrated a similar 50% reduction in maximum contraction of corpus cavernosum SM but only a 35% reduction for the aorta. However, the EC₅₀ for phenylephrine was actually increased more in the aorta than in the corpus cavernosum SM, opposite to the T1DM findings. Thus, at a similar time of DM, the reduction in SM contractility was greater in the corpus cavernosum SM compared with the aorta in both T1DM and T2DM rat models, which could fit with a mechanism of ED occurring prior to generalized vascular dysfunction. It seems reasonable to suggest an even earlier time point of approximately 2 or 4 weeks may be examined in the

future. In addition, Nangle et al., using mice after 4 weeks of streptozotocin-induced T1DM, found that the maximum contraction of the aorta to phenylephrine increased by 50% along with an increase of 0.85 log units in sensitivity [46]. However, no changes in phenylephrine contractility or sensitivity were reported for the corpus cavernosum. Thus, similar to the above Elçio İlu et al. study, aorta adrenergic contractility was higher relative to that of the corpus cavernosum in T1DM.

Clearly, changes in the endothelium can cause alterations in SM contractility and function, and these are detailed in the endothelium section. However, there can be changes that occur at the molecular level directly in the SM cells. In a T2DM animal model, Kovanecz et al. found that in vitro relaxation of corporal tissue from OZR rats was considerably less than that from lean Zucker (LZR) control rats [82]. Molecular analyses revealed that there was a considerable reduction in SM abundance and the SM cell/collagen ratio, as well as an increase in apoptosis, in the media of the penile dorsal artery of OZR rats compared with the LZRs, but there were no indications of cell proliferation (measured by proliferating cell nuclear antigen), transforming growth factor beta-1 expression, or the intima-media/lumen ratio. In the aorta of the OZR, in contrast to the penile dorsal artery, there was a reduction in proliferating cell nuclear antigen as well as a more pronounced decrease in the SM/collagen ratio, mainly from an increase in collagen, but there were no changes in transforming growth factor beta-1 or the wall/lumen morphometry. In the OZR rats, Western blots of aortic tissue confirmed the decrease in proliferating cell nuclear antigen and a reduction in the SM marker calponin. Thus, at 5 months of T2DM, there are at least some molecular changes occurring differently in the SM of the penile dorsal artery than the aorta. However, a shorter time of DM and/or temporal sampling over the duration of DM may be needed to tease out other early changes in the SM that may preferentially occur in the penile dorsal artery compared with the aorta or vice-versa.

More recently, Wei et al., utilizing a streptozotocin-induced rat model of T1DM, reported that the expressions of SM alpha actin and the more definitive markers of differentiated SM including calponin, SM myosin heavy chain, smoothelin, and myocardin were all significantly decreased at the mRNA level in the cavernous tissues of diabetic rats with ED compared with controls or diabetic rats without ED [79]. They also confirmed a significant decrease for SM alpha actin and SM myosin heavy chain at the protein level in diabetic rats with ED [79]. Furthermore, isolated corpus cavernosum SM cells also exhibited less contractility in a release collagen lattice assay. Thus, the diabetic rats that had ED demonstrated more of a change to the SM phenotype of the corpus cavernosum than rats that just had DM, which could be taken to suggest that a subset of diabetic rats is more sensitive to the pathology and develops an earlier ED. A future study with similar SM molecular characterizations of the aorta and the corpus cavernosum should be performed. More studies are also needed to delineate whether SM contractility is equally affected in different animal models of ED, as contradictory findings have been reported in the literature [46,49,50,79].

Even in animals without ED, it has been demonstrated that major differences exist in the molecular pathways that regulate SM contractility between the corpus cavernosum and other vasculature. For example, Jin et al. reported that PKC does not have a significant role in agonist-induced contractions in mouse corpus cavernosum SM, whereas it clearly mediates

the contractile response to agonists in the aorta [83]. Thus, one could hypothesize that this lack of PKC regulation may leave the corpus cavernosum SM more vulnerable to pathological processes than the aorta by removing a key regulator of SM contractility. Future studies should include analyzing PKC activity in both the aorta and corpus cavernosum SM during the temporal development of ED and also blocking PKC activity in the systemic vasculature in an animal model of ED.

Nangle et al. found that corpus cavernosum from inducible NOS (iNOS^{-/-})-deficient mice developed increased sensitivity to phenylephrine and an increased maximum electrical field stimulation-induced noradrenergic contraction of approximately 31% [84]. However, agonist-induced responses of aorta did not significantly differ between iNOS^{-/-} and control mice. These results suggest that iNOS-derived NO may play a role in modulating erectile function and confirm that iNOS does not play a significant role in macrovascular function under normal physiological conditions. This could again suggest an increased sensitivity of the corpus cavernosum SM to pathological insult as compared with the aorta. This same group also compared the in vitro contractility of corpus cavernosum and aorta from nNOS^{-/-} and eNOS^{-/-} mice. They reported that both corpus cavernosum and aortas from nNOS^{-/-} mice exhibited increased contractile responses to phenylephrine. In contrast, while corpus cavernosum from eNOS^{-/-} mice also exhibited increased contraction to phenylephrine, the aorta from these mice exhibited decreased contraction to this alpha agonist [85].

Conclusions

There is growing evidence for an association between ED and CVMD. Although the number of truly comparative studies performed on the SM of the corpus cavernosum and aorta, under identical conditions, is much more limited than that described for the endothelium, there is emerging data that point to a role of SM dysfunction as a key molecular mechanism mediating this link. However, more well-defined basic science studies involving a full-time course analysis after various interventions and challenges with respect to cavernosal SM and the internal pudendal artery, especially at earlier time points of ED, are needed to compare the corpus cavernosum with the more generalized vasculature, and in particular, the coronary arteries. These new data may lead to the discovery of novel and effective molecules and pathways for development as ED therapies and would profoundly impact the lives of millions of men after ED diagnosis.

Autonomic Regulation: Carol A. Podlasek, Anthony J. Bella

Introduction

The evidence for ED as a harbinger of CVD is based in large part upon a shared pathophysiology of endothelial dysfunction, with common risk factors including hypertension, dyslipidemia, smoking and DM, as well as clinical studies identifying risk of CVD in patients with ED [8]. ED commonly results from a combination of vascular and neuronal risk factors. In the absence of atherosclerotic disease in the penile bed, or as an additional pathophysiologic “hit” to erectile capacity, autonomic dysregulation may contribute to ED. In this section, we will examine the basic science evidence for a link

between ED and cardiometabolic dysfunction (including DM and metabolic syndrome [MS]) and identify gaps in knowledge that need to be filled in order to clarify this clinical link. In particular, we will focus on evidence linking ED and cardiometabolic dysfunction originating from the autonomic nervous system.

Autonomic Control of Erectile Function

Penile erection is a spinal reflex that can be initiated by stimuli from the periphery and from the central nervous system [86]. The balance between contractant and relaxant factors controls the degree of contraction of the SM of the corpora cavernosa and determines the functional state of the penis [86] by regulating blood flow into the erectile tissue. Autonomic fibers that innervate the penis are collectively called the cavernous nerve, and neural impulses travel through the cavernous nerve to effect penile vascular changes during erection and detumescence. Most processes that disrupt the autonomic innervation of the penis are not specific for sympathetic or parasympathetic fibers. Autonomic neuropathy, such as occurs in DM and after prostatectomy, is believed to be a leading cause of ED in the United States [87,88].

Autonomic Neuropathy/DM/MS

DM—Autonomic neuropathy is a leading cause of ED [89], particularly in diabetic patients, which is three times more likely to develop ED than non-diabetic men [90,91]. DM may affect any part of the autonomic nervous system including the genitourinary and cardiovascular systems [92]. Diabetic autonomic neuropathy can occur in patients with T1DM or T2DM. With T2DM, it has been reported to occur as early as within a year of diagnosis in patients [93] and may be present even before DM is diagnosed [94,95].

In animal models of DM, central and autonomic neuropathy is common [96,97]. The paraventricular nucleus of the hypothalamus is involved in centrally mediated erection. Four weeks after streptozotocin and vehicle injections, NMDA-induced erection, yawning, and stretch responses through the paraventricular nucleus were significantly blunted in diabetic rats compared with control rats [98]. The BB/WOR rat model of DM demonstrates both central and peripheral neuropathy with severe impairment of spinal sexual reflexes and peripheral neuropathic changes in hypogastric and motor pudendal nerve fibers [97].

Autonomic dysregulation has been defined in many disorders including DM, hypertension, and hyperlipidemia. The autonomic nervous system is divided into the sympathetic (fight-or-flight response) and parasympathetic (rest-and-digest) nervous system. Autonomic neuropathy results in increased sympathetic activity and decreased parasympathetic activity [99,100]. In T1DM and in prediabetic T2DM Goto-Kakizaki rats, increased levels of neuropeptide Y and noradrenaline were identified in autonomic nerves and increased calcitonin gene-related peptide in sensory nerves innervating the corpora cavernosa [101]. In keeping with this idea, increased concentration of the sympathetic neurotransmitter noradrenaline was observed in male genital organs in the months following induction of experimental T1DM in Wistar rats [102,103].

Synaptic transmission at parasympathetic pelvic ganglia neurons in control and chronic diabetic mice has been reported. In contrast to published data for sympathetic neurons, DM did not interrupt synaptic transmission at parasympathetic pelvic ganglia neurons from streptozotocin-treated wild-type C57BL/6J mice or diabetic db/db mice [104]. However, pelvic ganglia neurons from streptozotocin animals demonstrated longer after hyperpolarizations, and obese T2DM animals exhibited altered pre-synaptic regulation of neurotransmitter release. These animal studies are supported by reports in ED patients of increased sympathetic activity and decreased parasympathetic activity [105,106]. Giuliano and Rampin [107] suggest that sympathetic pathways play an anti-erectile role, while parasympathetic pathways play a pro-erectile role, supporting the idea that autonomic neuropathy in diabetic animal models contributes to the development of ED and endothelial dysfunction.

MS—Autonomic neuropathy is also common in patients and animal models of MS. Risk factors for MS are commonly associated with obesity and, when combined, significantly increase the risk of T2DM, CVD, and premature death [108]. MS is associated with autonomic sympathetic over-activity, through complex and incompletely elucidated mechanisms [109]. Animals with features of MS do not develop notable changes in cavernous autonomic nerve density or nerve-evoked SM activity. However, regeneration of nitrergic nerves after crush injury in rats with MS is impaired compared with injured controls. This manifests as a deficit in axonal regrowth and responses to axonal activation [110]. Nitrergic dysfunction and impaired neuronal NO signaling due to oxidative stress and nNOS uncoupling in penile arteries were observed in the insulin-resistant OZR, an experimental model of MS/pre-diabetes [111]. This dysfunction likely contributes to MS-associated ED along with endothelial dysfunction involving altered NO signaling [111].

Autonomic Nervous System and CVD

The autonomic nervous system regulates cardiovascular physiology, impacting the susceptibility of penile end organ dysfunction secondarily. Most organs, including the cardiovascular system, have some form of autonomic control, which requires sympathetic and parasympathetic input, while many blood vessels receive only sympathetic activity. Increasing sympathetic activity increases heart rate, while parasympathetic stimulation reduces cardiac activity. Cardiac autonomic neuropathy results in abnormal heart rate and vascular dynamics, which are features of heart failure [112]. Autonomic dysfunction can directly impact cardiovascular physiology causing cardiac autonomic dysregulation [113], and autonomic dysfunction has been identified in both diabetic and MS patients [113,114]. In diabetic animal models, it has been shown that insulin-dependent T1DM Akita mice exhibit reduced cardiac autonomic function and display a reduction in nerve density [115]. Glucose and insulin are potent stimulants of sympathetic activity. The high fat diet-fed streptozotocin rat, a model of hyperglycemia and insulin resistance, exhibits sympathetic nervous dysfunction in parallel with deteriorating myocardial systolic and/or diastolic function [116]. In MS animal models, altered GABAergic neurotransmission in the nucleus tractus solitarius and ventrolateral medulla have been identified, suggesting the importance of these regions in cardiovascular regulation [117]. Increased sympathetic modulation of vessels and heart precedes metabolic dysfunction in fructose-consuming mice [118]. Blood

pressure response to trimetaphane and heart rate response to metoprolol were greater in leptin-deficient ob/ob mice (model of obesity, hypertension, and MS) than in control littermates, indicating an activated sympathetic nervous system, and supporting a role for autonomic dysfunction in the pathogenesis of MS [119].

Both erectile function and the cardiovascular system are similarly controlled by sympathetic and parasympathetic divisions of the autonomic nervous system [120]. In support of this idea, an early study by Quadri et al. [121] found a significant association between ED and cardiovascular parasympathetic impairment. Phosphodiesterase (PDE)-5 inhibitors, such as sildenafil, are commonly used to treat ED. Sildenafil also increases sympathetic nerve activity in the cardiovascular system in conscious rats and acts on the central nervous system to increase sympathetic activity [122]. Reduced availability of NO is also common in ED and vascular diseases, including hypertension, hypercholesterolemia, and DM [123]. Chronic NOS inhibition with L-NAME elevates sympathetic nerve activity [124], supporting a common autonomic dysfunction in ED and CVD.

Conclusions

Vascular ED could help in detection of heart disease before development of symptoms [125,126], but can ED secondary to autonomic failure predict future development of cardiovascular autonomic neuropathy? While the risk factors for ED and CVD are similar and autonomic dysfunction and decreased NO occur both in the development of ED and CVD, it remains unclear whether ED development secondary to autonomic neuropathy can predict the development of cardiovascular autonomic neuropathy. With DM and MS, autonomic neuropathy appears to be a generalized systemic condition, and there is little basic science evidence to indicate whether the vascular bed of the penis and systemic vasculature react with the same time course and are equally sensitive to autonomic neuropathy. What data have been accumulated in this area are primarily clinical, and significant future study is needed both in animal models and in patients to determine how autonomic neuropathy affects known signaling pathways and tissue morphology relevant to erectile and cardiovascular function, and to define potential impact on end-organ function, morbidity, and mortality.

Hormones: Johanna L. Hannan, Noel N. Kim

Introduction

The primary focus in this section is to examine if testosterone is a unifying link between ED and CVMD. Despite the persistent view that exogenous testosterone may have adverse health effects [127,128], more recent analyses suggest that supplemental testosterone, maintained within the normal physiological range, does not contribute to the development of CVD [129]. Most clinical studies suggest an inverse correlation between serum testosterone levels and erectile function, as well as between serum testosterone levels and CVMD [127,128,130–135]. While these associations are substantive and provocative, causality is not proven, since the majority of the available clinical information is derived from retrospective and observational studies. We will summarize key findings from animal models

to assess the relationship between testosterone and CVMD or ED individually and as a whole.

Testosterone and CVD

Testosterone has been postulated to improve vascular function by acting as a vasodilator, mediating beneficial changes in vascular remodeling/arterial stiffness, and reducing or inhibiting inflammation, oxidative stress, and atherosclerosis [128]. Testosterone-induced vasodilation has been demonstrated in isolated animal and human blood vessels and involves the activation of rapid nongenomic signaling pathways [136–140]. A prominent nongenomic mechanism by which testosterone causes vasodilation is through hyperpolarization of vascular SM by stimulating large-conductance Ca^{2+} -activated K^+ channels (BK_{Ca} or MaxiK), voltage-activated K^+ channels (KV), and ATP-sensitive K^+ channels [138,141–147]. Testosterone can also inactivate L-type Ca^{2+} channels to prevent Ca^{2+} influx and thereby reduce SM tone [148–150]. Recent studies in endothelium-denuded porcine coronary arteries, denuded human umbilical artery, and cultured human vascular SM cells demonstrated that testosterone stimulates NO production by nNOS and ultimately activates BK_{Ca} and KV channels through cGMP-stimulated protein kinase G [144,151].

Testosterone has also been shown to cause vasodilation by acting on the endothelium. In both animal and human vascular tissues and cultured endothelial cells, physiologic concentrations of testosterone activate Ca^{2+} influx to stimulate NO production by increasing eNOS expression and eNOS phosphorylation through the cSrc/ PI_3K /Akt pathway [152–156]. In human endothelial cells, some of these effects appear to be directly mediated by the androgen receptor [155,156]. However, the importance of androgen receptor-mediated stimulation of NO function remains unclear, as testosterone can cause vasodilation in testicular feminized mice that lack androgen receptor [157]. Other studies have either found an estrogen-specific effect [158–160] or substantial aromatase activity in the endothelium with conversion of testosterone to estradiol and subsequent estrogen receptor activation that is required for stimulation of eNOS expression and phosphorylation [154,161].

In addition to influencing vascular tone, animal studies consistently show that testosterone has a protective effect against atherogenesis, decreasing platelet and monocyte adhesion, reducing expression of vascular adhesion molecules, and inhibiting plaque formation [152,162–166]. In human coronary artery endothelial cells, testosterone and dihydrotestosterone inhibited monocyte binding and expression of iNOS and adhesion molecules, while stimulating angiogenic behavior (tube formation) and increasing expression of phosphorylated eNOS [167].

Low testosterone has been related to increased oxidative stress in men [168], and testosterone replacement in symptomatic hypogonadal men reduced circulating levels of inflammatory cytokines [169]. Further, long-term testosterone treatment in men with low testosterone and angina symptoms reduced coronary artery intimal media thickness [170,171]. Remarkably, prostate cancer patients undergoing androgen deprivation therapy developed arterial stiffness within 3 months [172,173]. Thus, testosterone may inhibit some of the early processes leading to atherogenesis, such as oxidative stress and inflammation followed by vascular remodeling.

Testosterone and Metabolic Disease

Testosterone is an important regulator of body fat distribution, and low testosterone levels have been shown to be predictive of later development of metabolic disease and T2DM [131,174–177]. While not entirely consistent, the available clinical data demonstrate that testosterone replacement in hypogonadal men reduces central adiposity and insulin resistance, and improves lipid and inflammatory profiles [128,131–133,135,175]. Conversely, androgen deprivation therapy increases fat mass, low-density lipoprotein (LDL) cholesterol, triglycerides, and decreases insulin sensitivity [178]. These findings strongly suggest that testosterone is a common mediator of numerous facets of metabolic disease.

Low testosterone and metabolic disease may become a self-perpetuating condition, particularly in men with increased fat mass due to the activity of adipose tissue as an endocrine organ [171,179]. Increased aromatization of testosterone to estradiol in adipocytes leads to higher circulating estradiol levels that can in turn suppress testosterone production by inhibiting pituitary secretion of gonadotropins.

The main cellular mechanisms of insulin insensitivity are considered to be downregulation of the glucose transporter GLUT4 and insulin receptor, as well as increased phosphorylation of insulin receptor substrate (IRS-1). Testosterone has been shown to upregulate both GLUT4 and the insulin receptor [180–182]. In a human liver cell line, insulin receptor mRNA was significantly increased, and glucose oxidation was elevated in response to testosterone treatment [183]. In castrated rats, GLUT4 expression was decreased and phosphorylated IRS-1 was increased, while testosterone supplementation normalized levels of phosphorylated IRS-1 in muscle, liver, and fat tissue [180].

Thus, testosterone influences body fat content, steroid hormone and adipokine levels, insulin sensitivity, and glucose metabolism. Low testosterone states may lead to metabolic dysregulation due to multiple and self-perpetuating mechanisms that overlap considerably with cardiovascular pathology. This is supported by limited data in men with metabolic disease who have a higher risk to develop CVD [184,185].

Testosterone and ED

Hypogonadism can affect any of the critical events of erection, including neuronal activation of arterial flow into the penis, relaxation of the corporal SM, and veno-occlusion [186]. Testosterone can impact the initiation of erections by altering the release of brain neurotransmitters such as dopamine, oxytocin, or NO from the medial preoptic area [187,188]. Animal models have shown that circulating androgens are necessary for the maturation, development, and preservation of the pelvic sympathetic neurons that supply the penis [189–191]. Furthermore, androgens are neuroprotective and required for nerve regeneration following nerve injury [192,193]. These findings have important implications for men suffering from ED after radical prostatectomy who are either hypogonadal or are undergoing androgen deprivation/receptor antagonist therapy.

Castrated rodents and men with low testosterone demonstrated alterations in endothelial morphology, decreased trabecular SM content, increased extracellular matrix deposition, and a loss of elastic fibers in the tunica albuginea [194–197]. Additionally, adipocyte

accumulation within the subtunical regions of the corpora cavernosa in castrated rabbits has been postulated to lead to impaired veno-occlusion [195]. These changes in corporal structure and function are prevented or reversed when testosterone is replenished in animals and erections are significantly improved [194,195,198,199]. The data in humans are much more limited, but are consistent with animal studies. Significant decreases in the SM and increases in collagen have also been observed in penile tissue from men undergoing androgen suppression prior to gender reassignment surgery [200] and aged men with hypogonadism [200,201]. Yet the molecular mechanisms that mediate these cellular and tissue structure changes are not well understood, and postulated regulation by cytokines/ growth factors and pluripotent cell differentiation pathways remain largely untested.

Testosterone also plays a role in the function of penile arterial and cavernous SM [78]. Testosterone and dihydrotestosterone can cause direct relaxation of penile arteries and cavernous tissue [202–204], and androgen deficiency has been demonstrated to decrease the expression and enzymatic activity of eNOS, nNOS, and PDE5 and increase alpha-adrenergic responsiveness in the penis [198,205–208]. In an animal model of cardiometabolic syndrome, testosterone supplementation reduced visceral obesity and improved penile responsiveness to PDE5 inhibitors [209]. Additionally, clinical studies have demonstrated the beneficial effect of combined PDE5 inhibitors and testosterone treatment on improving erectile function in men with hypogonadism, although this remains debated [210–212]. Testosterone's effect on increased PDE5 expression is not understood as it has been shown that androgen response elements do not appear to be present in PDE5 promoter regions, and androgens had no effect on PDE5 expression in cultured cavernous SM cells [213,214]. Whether testosterone-related changes in PDE5 are due to actual transcriptional regulation or changes in SM content requires further exploration.

Link Between Testosterone, CVMD, and ED?

Although there are many studies examining the role of testosterone in CVMD or ED, there are few that look at its contribution to the development of all three disease states concurrently. Altogether, preclinical and clinical data strongly suggest that low testosterone is a risk factor for CVMD and ED; however, whether symptoms of CVD or ED manifests first remains to be elucidated. Further studies are required in which a time course of erectile function and cardiovascular health is evaluated in animal models of low testosterone. The unique aspect of this topic is that there is a growing body of interventional clinical study data in men with prostate cancer undergoing androgen deprivation. Assessing erectile function and cardiovascular symptoms in these men will be important to assess if testosterone is driving the CVD and ED.

Conclusions

Although the body of evidence of testosterone's contribution to CVD or ED is impressive, there remain many questions. Further studies are required to demonstrate the role of testosterone in the development of CVD and ED. Additionally, important mechanistic questions remain to be answered, including: (i) how testosterone regulates atherogenesis, growth factor expression, and calcium flux; (ii) differentiating the specific actions of testosterone, dihydrotestosterone, and estradiol; and (iii) how the effects of androgens and

their metabolites may differ in human versus animal tissues. The clinical benefits of testosterone should be interpreted cautiously. A recent meta-analysis of randomized, placebo-controlled trials evaluating testosterone therapy and cardiovascular events in almost 3,000 men suggested that industry-funded studies demonstrated a more favorable cardiovascular event outcome [215]. In other meta-analyses, any increase in the risk of cardiovascular events was considered to be either statistically or clinically insignificant [216,217]. Further, in a prospective evaluation of elderly men enrolled in the Framingham heart study, no association was found between sex steroid levels or gonadotropins and clinical manifestation of incident CVD or risk of all-cause mortality over a 10-year period [218]. Thus, the potential health benefits of testosterone may be numerous, but it remains unclear whether any single hormone or factor by itself can significantly impact the occurrence of multi-factorial outcomes such as CVD or all-cause mortality.

Metabolics: Nestor F. Gonzalez-Cadavid, Kelvin P. Davies

Introduction

Metabolism refers to the chemical transformations occurring within cells that create energy to drive cellular functions and generate the chemical building blocks that allow cells to grow, reproduce, maintain their structures, and respond to their environments. Clearly, this definition suggests that any disease disturbing normal cellular metabolism will likely result in pathology. In the case of erectile and cardiovascular tissue, systemic metabolic diseases, such as MS, DM, and obesity, are associated with the development of ED and CVD, respectively. However, the different physiological function and environment of cells in the heart, vasculature, and erectile tissue suggest that potentially, there are differences in both their normal metabolism and in their susceptibility, mechanism, and resulting pathology in response to metabolic diseases. We review the literature for evidence of shared pathological changes in metabolism that might lead to development of ED and CVD in an attempt to identify common mechanisms for the development of these diseases.

Accepted Tenets for Development of ED and CVD

The presently accepted tenets for the association between ED and CVD resulting from metabolic disease are that [219–222]: (i) the main metabolic alterations are shared between erectile and cardiovascular tissue; (ii) the penile corpora cavernosa is an extension of the vascular system, and hence, a similar disturbance of physiologic function leads to the development of ED and CVD; (iii) both ED and CVD have a main vasculogenic component; (iv) endothelial dysfunction and atherosclerosis are major contributing factors in the development of both ED and CVD; and (v) the effects of hypogonadism (late-onset hypogonadism; i.e., low serum testosterone) on metabolism contribute significantly to both ED and CVD etiology and pathophysiology.

Premises (i)–(iii), and to a certain extent (v), have substantial clinical and experimental support, or are even axioms. Indeed, there is a consensus based on this evidence, mostly at Level 1, Grade A [35], that among other facts: (i) a large number of men with ED have early signs of CAD that may progress to more severe CAD compared with men without ED; (ii) the time elapsing from ED symptoms and CAD symptoms and cardiovascular events is

approximately 2–3 and 3–5 years, respectively; (iii) men with ED should have the hypertension, DM, and hyperlipidemia treated aggressively; and (vi) total and free testosterone should be measured in all men with ED.

Pathophysiological Effects of Metabolic Diseases

Metabolic diseases have in common system-wide effects on glucose and oxidative metabolism. With hyperglycemia, there is increased generation of advanced glycation end products in both cardiac and erectile tissue which results in protein damage, directly having a deleterious effect on cellular function and activating several pathologic down-stream pathways [223]. For example, in an animal model of diabetes, hyperglycemia increases O-GlcNAc modification of eNOS in the penis [224], preventing phosphorylation at the primary positive regulatory site on the enzyme which would be expected to impair the erectile response. Similarly, several studies have linked hyperglycemia to increased O-GlcNAc levels in cardiac tissue resulting in impaired contractility, mitochondrial dysfunction, and metabolic dysfunction [225]. Overall, in cardiac (compared to erectile) tissue, there is a far broader knowledge of the protein targets for O-GlcNAcylation such as transcription factors that regulate cell survival [226] and many proteins that play a key role in metabolic regulation, such as AMP-activated protein kinase, IRS1/2, Akt, and GLUT4 [227,228].

Another shared consequence of hyperglycemia is that in both erectile and cardiac tissue, there is increased oxidative and nitrosative stress [229], which can effect vascular homeostasis, disrupt cellular enzymatic function, and activate fibrotic pathways. On the other hand, despite the substantial evidence of dyslipidemia contributing to the cardiovascular complications of MS, T2DM, and obesity [230], related studies on ED have lagged significantly, stemming from the unsubstantiated assumption that hyperglycemia alone and its metabolic consequences are the main factors causing ED in these conditions. Therefore, mechanistic research rather than the mere induction of ED with hypercholesterolemic or high fat diet is needed to clarify this important issue. Recently, it has been recognized that metabolic diseases are often associated with high levels of uric acid, a product of purine metabolism [231]. Uric acid has been shown to contribute to cellular oxidative stress, increase arginase activity, and directly scavenge NO. Blood levels of uric acid are increasingly recognized as a marker for CVD, and recent evidence suggests uric acid is also a potential marker for ED [232].

Evidence for a Common Role for Endothelial Dysfunction and Atherosclerosis in the Development of Both ED and CVD

The premise that endothelial dysfunction and atherosclerosis are major contributing factors in the development of both ED and CVD is somewhat controversial, and more an extension of views in the cardiovascular field than evidence-based observations on ED patients or animal models. For instance, endothelial dysfunction, that is measurable and rather significant in CVD, is only inferred to affect the penile corpora cavernosa from systemic measures [222], and in fact has not been demonstrated to be a major contributing factor for ED in men or animal models. The relative minor role of endothelial dysfunction in most forms of ED can be understood though evidence suggesting the endothelium, and specifically eNOS, plays only an ancillary role in erectile function. In addition, endothelial

damage, with its significance for the formation of neointima and arterial wall plaques in atherosclerosis, is not necessary for corporal SM fibrosis, the main non-neurogenic process impairing corporal SM relaxation [233,234] that is a potential target for the continuous long-term use of PDE5 inhibitors [235–237]. Studies in animal models of DM demonstrate that endothelial cell–cell junctions in cavernosal tissue have significantly increased permeability compared with other vascular tissues, and this may account for the reason that ED precedes other vascular diseases caused by DM [72].

The assumption that atherosclerosis is a significant factor in ED [35,219,220] also needs to be treated with circumspection. Oxidative modification of LDL to ox-LDL is believed to be major cause of endothelial dysfunction through development of atherosclerosis [238], and levels of ox-LDL increase with metabolic disease [239]. Increased levels of ox-LDL are both a marker for ED and CVD [240]. Because of the association between LDL, atherosclerosis, and CVD, statins are often given to patients to lower LDL cholesterol and prevent the formation of atherosclerotic plaques and are now widely accepted as preventative of CVD [241]. Although recent reviews have suggested a clinically relevant improvement in erectile function in men given statins [242–244], several previous reports have described no such improvement, or even a negative effect [245]. The use of statins to provide evidence for the role of atherosclerosis in the development of ED is complicated by the possibility that there are several pleiotropic effects of statins, such as improving anti-oxidant mechanisms and enhancing NO availability, and by reports that statins lower testosterone levels [246]. However, there is evidence that changes in the lipid chemistry of blood may have direct effects on erectile function without involvement of atherosclerosis. For example, ox-LDL can have a direct effect on cavernous SM tone [247], and hypercholesterolemia has been associated with increased arginase activity in corporal tissue (an enzyme metabolizing arginine and thereby reducing NO availability) [248].

The detection of hemodynamic alterations presumably due to plaque obstruction of blood flow into the corpora and the stenosis induced by the increase in intima/media thickness may explain arterial insufficiency but not the most prevalent form of ED (i.e., corporal veno-occlusive dysfunction) where the corporal SM inability to relax and compress the veins against the rigid tunica albuginea is the real cause of ED [233–237]. Recent evidence indicates that the corporal vascular and trabecular system does not necessarily behave identically to the cardiovascular system. Atherosclerosis was found in only 13% of penile autopsy tissue, whereas coronary and peripheral atherosclerosis was present in about 80% of the examined cases [249]. This is in contrast with the observed increase in cavernous intima/media thickness in ED patients [250], that although is considered to be a landmark of atherosclerosis may also occur in arteriosclerosis or arterial stiffness [251]. These reports necessitate reexamination of the widely accepted concept that endothelial dysfunction and atherosclerosis are linked to the development of vasculogenic ED and act as putative triggering factors for this condition. This is particularly in the light of the nearly forgotten process in vascular wall pathology, the role of arteriosclerosis or arterial stiffness [251] due to the fibrosis, and loss of SM in the media (not to atheromatosis) seen in aging and T2DM, which is essentially similar to the corporal fibrosis in veno-occlusive dysfunction [82].

Hypogonadism as a Common Factor in Development of ED and CVD

Although late-onset hypogonadism associated with MS and T2DM may contribute to both ED and CVD, another field of controversy regards the value of testosterone replacement to ameliorate MS and ED, and to a certain extent improve these symptoms, particularly insulin resistance and visceral fat accumulation. In overt hypogonadism, convincing evidence is lacking that it can correct ED associated with late-onset hypogonadism, even in conjunction with PDE5 inhibitors. The results of the trials are heterogeneous and limited by small sample sizes, and have not provided a definitive answer as to whether low testosterone plays a key role in the development of ED and CVD or is simply associated with these processes [252].

Metabolomics to Elucidate Common Metabolic Mechanisms in the Development of ED and CVD

Perhaps one of the most promising avenues for determining comparative metabolic changes occurring in CVD and ED is the development of “metabolomics” technology. “Metabolomics” is defined as the quantitative determination of chemical process involving metabolites [253]. The technique involves rapidly halting metabolic processes in a tissue (by flash freezing), and isolating and separating metabolites (most commonly by gas chromatography, liquid chromatography, and capillary electrophoresis followed by identification and quantification of metabolites by mass spectroscopy or nuclear magnetic resonance) [253]. The technique has already been widely applied to CVD, and several studies have provided a detailed overview of the metabolic profile in cardiac tissue, identifying potential biomarkers for myocardial ischemia and cardiogenic shock, risk of developing atherosclerosis or future cardiovascular events, atrial fibrillation, chemotherapy-induced cardiotoxicity, and pulmonary hypertension related to advanced heart failure [254–256]. If similar studies were to be performed on erectile tissue, investigating the changes in the metabolic profile that occur with the development of ED, this may give great insight into the association between ED and CVD.

Conclusions

Although cells from both erectile and cardiovascular tissue share common metabolic pathways, these pathways are tailored to specific physiologic functions. It is likely therefore that the development of ED and CVD will share some common changes in metabolism resulting in pathological mechanisms. There is strong evidence that in both ED and CVD generation of advanced glycation, end products and oxidative stress are contributing factors, but little is known on the contribution of dyslipidemia alone or in combination with hyperglycemia. However, the role of changes in endothelial function, particularly caused by hypercholesterolemia through the development of atherosclerotic plaques, although accepted as a mechanism in CVD remains contentious in the pathophysiology of ED. “Metabolomic” technology has generated a complex detailed overview of the metabolome in cardiovascular tissue and the changes that occur with CVD, but as yet, this technology has not been applied to changes occurring in the development of ED in the corpora cavernosa and the pelvic ganglion.

Summary Remarks: Trinity J. Bivalacqua, Arthur L. Burnett

The Basic Science Committee of the SMSNA has reviewed the scientific literature from multiple disciplines and provided the current evidence for a mechanistic link between ED and CVMD. As summarized in this state-of-the-art review, there are many questions that are still unanswered as it relates the mechanistic link between ED and CVD. There is a plethora of reports in the literature that suggests a strong link between ED in young men and subsequent cardiac disease. However, as we have highlighted in this report, the true mechanistic understanding of ED and subsequent CVMD is far from complete.

The International Society of Sexual Medicine and now the American Urological Association (AUA) and its associated research division the Urology Care Foundation have made the investigation, characterization, and development of therapeutics for the treatment of sexual dysfunctions to be a top priority. This is outlined by the National Urology Research Agenda highlighting sexual dysfunction as a priority research area for advancing urologic health. Recently, the SMSNA has teamed up with the AUA Urology Care Foundation to fund sexual medicine research in both male and female sexual dysfunctions each year. With technology and methods to study disease processes at the genomic level and correlate pathologic disease outcomes, we will be able to better define links between specific diseases such as ED and CVMD.

Our panel of sexual medicine scientists acknowledge the association; however, we have highlighted the gaps in our knowledge and areas of future scientific investigation in order to develop a better understanding of this link which will undoubtedly lead to future therapeutic targets for these disease processes. To address some of these gaps in knowledge, we submit our top recommendations for future research in this area.

- A. For endothelial cell biology, future areas of research should critically evaluate mechanisms unique to penile endothelial cells, which underlie the apparent temporal relationship between penile and systemic vascular beds in response to cardiometabolic risk factors.
- B. For SM cell biology, the temporal time-dependent effects of risk factors for CVMD and deterioration of the internal pudendal artery smooth musculature and subsequent corporal SM dysfunction are not well described and should be investigated in greater depth to show time-specific associations, which have only until now been correlative. These studies should be performed in concert with measurements of coronary and cardiac myocyte changes to further elucidate tissue-specific changes between the penile and coronary vasculature.
- C. For autonomic dysfunction, the majority of the causal link is purely epidemiologic and establishes associations in patient clinical outcome cohorts. Although these data provide important information, rigorous preclinical studies are needed to determine how autonomic neuropathy affects known signaling pathways and tissue morphology relevant to erectile and cardiovascular functions. These studies are essential to understand the temporal causal relationship between CVMD and autonomic dysfunction of the penile circulation.

- D.** For testosterone deficiency, the link between low testosterone and subsequent development of ED and CVMD is robust. However, there are a number of key questions (androgen effects on peripheral tissues and the differences between rodents and humans; is testosterone, DHT, or estrogen the main culprit involved in subsequent ED and CVMD risk?) raised by our experts which warrant further investigation. This is a hot topic of discussion, and this panel will continue to pursue this topic in future reports and white papers.
- E.** For metabolic pathways involved in development of ED and CVMD, our experts highlight studies of the “metabolome” in penile circulation and corpora cavernosa are needed to compare with the well-established understanding of metabolomics in cardiac dysfunction as this may shed light into causal and temporal relationships of ED development in CVMD.

In summary, our panel of sexual medicine scientists has defined and captured our current state-of-the-art understanding of ED and CVMD and highlights future areas of both basic science and clinical research in this field.

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Figure 1.

Overview of the cardiometabolic risk factors that can influence endothelial function resulting in discrete and observable outcomes common to all vascular beds but may be intrinsically more sensitive in the penile vasculature