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REVIEW PAPER

Cardiometabolic Disorder and Erectile Dysfunction

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Abstract

Erectile dysfunction (ED), which is defined as the inability to attain and maintain a satisfactory penile erection to sufficiently permit sexual intercourse, is a consequence and also a cause of cardiometabolic disorders like diabetes mellitus, systemic hypertension, central obesity, and dyslipidemia. Although there are mounting and convincing pieces of evidence in the literature linking ED and cardiometabolic disorders, impairment of nitric oxide-dependent vasodilatation seems to be the primary signaling pathway. Studies have also implicated the suppression of circulating testosterone, increased endothelin-1, and hyperactivation of Ang II/ATIr in the pathogenesis of ED and cardiometabolic disorders. This study provides comprehensive details of the association between cardiometabolic disorders and ED and highlights the mechanisms involved. This would open areas to be explored as therapeutic targets in the management of ED and cardiometabolic disorders. It also provides sufficient evidence establishing the need for the management of cardiometabolic disorders as an adjunct therapy in the management of ED.

Keywords Erectile function · Diabetes · Dyslipidaemia · Hypertension · Male infertility · Obesity

Background

Erectile dysfunction (ED), defined as the inability to attain and maintain a satisfactory penile erection to sufficiently permit sexual intercourse [1], serves as a boundary between sexual dysfunction and other male sexual disorders. Though ED seems benign, it exerts a psycho-social impact, resulting in reduced quality of life for the patients and their partners [2]. ED is convincingly associated with predisposing factors and attendant adverse health conditions. Compelling shreds of evidence have established links between ED and cardiometabolic disorders [3]. ED has also been correlated with incident coronary artery disease [4], establishing ED as an early indicator of cardiometabolic disorders and cardiovascular disease. Hence ED may serve as a biomarker and window of curability for cardiometabolic disorder. However, this may be quite difficult because individuals usually shy away from discussing their sexual problems even with their physicians [5].

Cardiometabolic disorders such as diabetes, hyperlipidemia, hypertension, and obesity do not only promote vascular dysfunction, but they also serve as risk factors for the development of ED. Although ED is associated with cardiometabolic disorder via several mechanisms, the primary mechanism is vascular insufficiency such as atherosclerosis and endothelial injury [6]. The impairment of nitric oxide-mediated endothelium-dependent vasodilatation and vascular insufficiency are similar pathways in the pathophysiology of ED and cardiometabolic disorder [7, 8].

This study provides details on the mechanisms linking ED and cardiometabolic disorder. This would open areas to

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be explored as therapeutic targets in the management of ED and metabolic disorders. It also provides sufficient evidence establishing the need for the management of cardiometabolic disorders as an adjunct therapy in the management of ED.

Cardiometabolic Disorders

Cardiometabolic disorder is a group of metabolic risk factors for atherosclerosis such as insulin resistance or diabetes mellitus, systemic hypertension, central obesity, and dyslipidemia [9]. These predisposing factors contribute significantly to the global mortality and morbidity rate and hence remain a public health issue. Cardiometabolic disorder may be a consequence or cause of ED. Studies have established the role of arterial thickening and atherosclerosis, vascular endothelial damage, and remodeling in the pathogenesis of cardiometabolic disorder [10, 11]. The roles of antioxidants and oxidative stress in endothelial injury and cardiometabolic disorder have also been documented [9, 12]. These factors are also essential in the aetiopathogenesis of ED.

Erectile (dys)function: Physiology and Pathophysiology

Physiology of Erection

The regulation of normal penile erection involves a coordinated interplay of molecular mechanisms and several physiological events. These networks of events have been broadly categorized as neurological, vascular, and tissue responses [13]. An alteration in these events might potentiate an imbalance and consequently result in ED. The events are either controlled by some biogenic mediators responsible for erection or regulated by hormones, thereby suggesting that the regulation of penile erection can either be hormonal or non-hormonal dependent [14]. The control of penile erection is primarily initiated or triggered by the integration of visual, tactile, olfactory, and imaginative responses. This control is coordinated by specific regions in the brain such as the paraventricular nucleus, anterior hypothalamic nuclei, and medial pre-optic areas that are located in the hypothalamus to regulate erection and modulate autonomic events associated with sexual responses. The nerves that control erectile activity in the penile tissue stem from the autonomic system which is made of both sympathetic and parasympathetic fibers. The erectile activity is usually controlled by signaling of the autonomic fibers network to the penis and as well as somatic fibers pathways to the perineal striated muscles which in turn are responsible for penile sensation. The central and peripheral transmitter systems control the balance between contraction and relaxation of cavernosal smooth muscles to facilitate and maintain penile erection. During erection, blood flows through the internal iliac artery branch and other accessory arteries to regulate the central and peripheral sinusoids [15]. Although numerous neurotransmitters, neuropeptides, hormones, and molecular mediators contribute either directly or indirectly to penile erection. The roles of dopamine, serotonin, norepinephrine, oxytocin, prolactin, acetylcholine, and nitric oxide have been well-established in the control of penile erection [16]. These mediators have been documented to influence the release of nitric oxide consequent to the activation of erectile tissue through the non-cholinergic fibers (nNos) and endothelial lining (eNos) which is considered the major molecular mediator responsible for penile erection [17–19]. Nitric oxide is widely expressed at the cellular level and activates the guanylate cyclase to increase the production of cytoplasmic cyclic guanosine monophosphate which in turn relaxes the smooth muscle by lowering the levels of intracellular calcium [17, 20] and ultimately facilitates penile erection. Meanwhile, a surge in intracellular calcium levels has been connected with the contraction of corpus cavernosal smooth muscle cells and consequently implicated in penile flaccidity. The phosphodiesterases are enzymes known to increase the cytoplasmic calcium levels in smooth muscle cells of corporal cavernosal tissue via hydrolysis of cyclic GMP- an enzyme responsible for the relaxation of corpus cavernosum cells.

Besides, the involvement of androgens in the regulation of penile erection has been well established. It has been documented that androgens mainly testosterone may influence erectile function via both central and peripheral effects, especially in the maintenance of libido.

In summary, penile erection involves a coordinated balance between the factors responsible for the contraction and relaxation of cavernosa muscles thereby regulating the blood flow to penile tissues.

Pathophysiology of ED

ED (ED) is a pathological phenomenon characterized by the inability of sufferers to develop and/or maintain an erection sufficient enough for satisfactory sexual performance [21]. The etiological basis of ED can often be linked to various levels of interruptions in the mechanism of erection including but not restricted to low levels of nitric oxide (NO) and cyclic Guanosine Monophosphate (cGMP) within the smooth muscles of the penile shaft. Additionally, ED has been reported to occur as a result of vascular, neurologic, psychological, and hormonal factors [22], among others. In the period preceding the current deepened research interest in ED, it was erroneously believed to be purely psychogenic aetiopathogenesis, however, the

majority of cases are now reportedly linked to specific organic causes [23].

The pathophysiology of organic ED can be discussed under the two broad etiological classes, namely endocrine and non-endocrine causes. The non-endocrine causes are the commonest and include pathologies that are vasculogenic, neurogenic, or iatrogenic in origin [23].

Vasculogenic ED occurs as a result of anomalies affecting either or both blood inflow through the penile arteries or penile blood drainage through the veins and these have been reported to account for the majority of organic ED [24]. Atherosclerotic narrowing in the caliber of the penile arteries and arterioles impedes blood inflow thereby interfering with the massive blood filling of the corpus spongiosum and corpus cavernosum muscles required for a normal process of erection. On the other hand, the pathology can also be venogenic in which case the filling occurs normally but the blood is not sufficiently retained within the penile structures due to premature venous leakage, a condition described as a veno-occlusive dysfunction [25]. Additionally, atherosclerosis alongside most other cardiovascular disorders including hypertension, reperfusion injuries [26], and heart failure are said to have correlations with reduced nitric oxide (NO) production thereby predisposing to ED via an incapacitation of the NO pathway of erection [27]. The NO deficiency in this class of patients appears to be a direct consequence of prolonged ischemia and hypoxia occasioned by atherosclerotic stenosis or other flow-limiting cardiovascular events which invariably result in a reduction in activities of Nitric Oxide Synthase (NOS) within the penile arteries [28]. The strength of the correlation between cardiovascular disorders and ED is such that, the diagnosis of ED in any individual is seen as an indication of an underlying cardiovascular disorder [29].

The confirmation of any case of ED as neurogenic is always a daunting task for several reasons. Erection is a neurovascular process and the identification of a neural pathology in any case of ED does not exclude the possibility of a co-existing or even pre-existing vasculogenic component [30]. Any disorder affecting any of the nervous system structures involved in the mediation of the process of erection such as the pudendal nerve, cavernous nerve, spinal cord, hippocampus, and the hypothalamus among other structures is capable of inducing ED. The extent, nature, and severity of ED of neurogenic origin depends largely on the neurological structure affected and the anatomical location of the lesion [31].

Iatrogenic ED are those occurring as a result of the actions and inactions of a medical practitioner during the course of management. Several medications have been associated with ED. Prominent among these drugs are antihypertensives like thiazide diuretics, androgen antagonists, antipsychotics, opiates, digoxin, and some anti-ulcer drugs [23]. Often, the mechanism underlying the ED in these cases is not well defined and it remains difficult to discern whether or not it has a link with the primary illness being managed. It is also not uncommon to find ED occurs as a complication of some penile surgeries or surgical procedures around the perineum. Surgical operations occasioning direct destruction of penile tissues, the blood supply, or nerves are common causes of ED [32]. ED due to damage to the cavernous nerve following a radical pelvic operation has been described as the commonest type of iatrogenic ED [33]. The damage after most surgical procedures is mostly neurogenic in nature, however, additional vascular components are not uncommon.

The endocrine disorders that are commonly associated with the development of ED include hypogonadism (Subnormal testosterone level), thyroid dysfunction, hyperprolactinemia, and diabetes mellitus (DM) [34].

Explaining the role of testosterone in ED is far more complex than a mere consideration of the serum levels in any particular individual. Contrary to the report that a minimum serum level of testosterone of about 8 nmol/l is required for normal erectile function, some hypogonadal men have been reported to exhibit an almost normal sexual performance despite testosterone levels below this value [35]. It is now clear that other factors, including age, comorbidities, and level of luteinizing hormone among others play a vital role in determining the effect of hypogonadism on erectile function. Whereas evidence abounds to confirm the dependence of erectile function on adequate androgen levels, the extent of hypogonadism sufficient to induce ED remains a source of controversy [36]. The normal adult male testosterone level is believed to be unnecessary for normal erection and additional exogenously administered testosterone often does not improve the quality of erection [36].

The thyroid gland is a very important organ in the body whose hormone exhibits its effect on virtually all cells of the body. A large percentage of men with thyroid diseases, including either hyperthyroidism or hypothyroidism have been reported to suffer ED [37]. This is linked to reduced libido, fatigue, and depression which are common symptoms of thyroid dysfunction and are capable of impacting general sexual performance in both male and female sufferers [38].

High levels of blood prolactin (hyperprolactinemia) from pituitary adenomas is another rare cause of hypogonadism due to the overwhelming negative feedback suppression of gonadotropin-releasing hormone by the high prolactin level which inadvertently results in low levels of luteinizing hormone, low testosterone levels and ultimately ED [39]. It is therefore imperative to evaluate serum prolactin and luteinizing hormone levels in any case of ED where the serum testosterone level is found to be abnormally low.

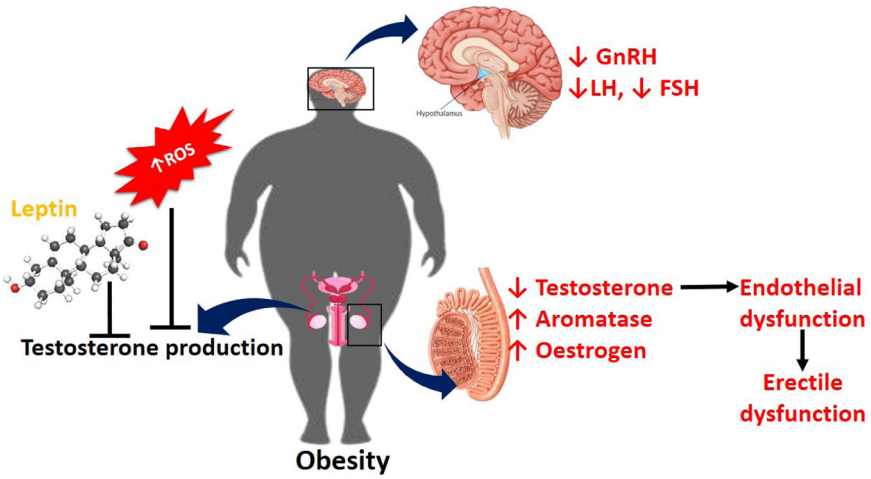

Fig. 1 Schematic illustration of the mechanisms linking obesity with erectile dysfunction. Obesity is associated with increased leptin levels and enhanced reactive oxygen species (ROS) generation, which in turn reduces testosterone levels. Obesity also suppresses the hypothalamic-pituitary-testicular axis, leading to reduced levels of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), thus, reducing testosterone production. This causes endothelial dysfunction and results to erectile dysfunction

Diabetes mellitus is commonly complicated by various forms of vasculopathies and neuropathies and men with DM have been described as being at a higher risk of developing ED. The risk of ED is reportedly higher in type 2 DM than in type 1 DM with prevalence rates of 66.3% and 37.5% respectively [40]. The pathophysiological basis of ED in DM is complex and multifaceted. Hyperglycemia induces a systemic oxidative stress which results in a cascade of events that lead to a reduction in the amount of NO produced, hypercoagulability state, pro-inflammatory state, vasoconstriction, and ultimately ED [41]. Additionally, the microvascular, macrovascular, and neurologic complications of DM and the numerous comorbidities like dyslipidemia, hypogonadism, hypertension, obesity, and even depression constitute major predisposing factors to ED [42].

Obesity and ED

Obesity is a condition characterized by excessive accumulation of fat in the body. It is commonly defined quantitatively as a body mass index (BMI) of 30 kg/m^2 or more while BMI between 25 and 29.9 kg/m^2 is referred to as overweight [43]. Obesity has been reportedly associated with the increased prevalence of many cardiovascular risk factors including type 2 DM, hypertension, dyslipidemia, and sleep disorders, and has been directly implicated in cases of cardiovascular diseases [44]. It is a major part of metabolic syndrome which in turn has been reported to be closely associated with ED [45]. The relationship between obesity and ED is rather complex and not understood, however, both conditions are believed to share a similar pathophysiological environment that is defined by inflammation and oxidative stress together with the eventual insulin and leptin resistance that result from them [45]. The controversy trailing the connection between the two disorders is further deepened by the inconsistent reports on the effects of weight loss on the erectile function of overweight men [46]. There is however a pathophysiological connection between obesity and ED which is multifaceted and can be viewed via several varied pathways (Fig. 1).

The pathological basis of obesity is a system phenomenon rather than a local adipocyte anomaly, involving elevated blood lipids and adipokines which induces inflammation in adipose tissues that eventually results in leptin and insulin resistance [47]. This induces widespread inflammatory response and oxidative stress in body tissues including the hypothalamus thereby affecting the metabolic as well as neuroendocrine regulatory functions [45]. The impact of this effect on the hypothalamic production of gonadotropin-releasing hormone incapacitates the hypothalamus-pituitary-testes axis leading to low levels of testosterone that may be a cause of ED. Additionally, the elevated blood levels of leptin also have a direct inhibitory effect on testicular production of testosterone [48], and a negative correlation has been established between BMI and serum testosterone level as well as erectile function [49].

Endothelial dysfunction secondary to some of the complications of obesity is another important pathological interface between obesity and ED. Amongst other features, endothelial dysfunction causes a reduction in NO production due to oxidative stress-induced suppression of nitric oxide synthase in the endothelium [50]. Essentially, the features of obese individuals that predispose them to endothelial dysfunction include inflammation, oxidative stress, elevated adipokines, and free fatty acids.

Generally, ED has been reported to be prevalent in diabetic men who are obese and the key connecting

pathologies among these disorders include endothelial dysfunction, macrovascular disorders, and hypogonadism [51]. In the management of ED, weight loss has been found to play an important therapeutic role as an adjuvant to drug treatment [46]. This further underscores the importance of obesity or excessive body fat accumulation in the pathophysiology of ED.

Diabetes and ED

Diabetes, a metabolic disorder diagnosed by a persistent increase in blood glucose concentration, often results from a lack of insulin synthesis (type-1) or resistance to insulin by glucoregulatory organs (type-II). This metabolic disorder affects over 463 million adults globally, with increasing incidence of obesity, aging, and uncontrolled lifestyle changes [52]. Despite giant strides over the decades, a completely effective treatment regimen has not been established, due to the multiple pathogenic pathways implicated in the etiology of this disorder. Thus, the available therapeutic strategy depends on prophylaxis targeting hyperglycemia to improve glucose metabolism and delay the onset/progression of complications. However, poorly managed diabetes is associated with both microvascular (neuropathy, nephropathy, and retinopathy) and macrovascular (cardiovascular dysfunction, peripheral vascular disorder, and stroke) complications, thereby exerting a heavy toll and reducing the quality of life among patients [53, 54]. These complications are associated with structural and functional derangement in the tissue due to hyperglycemia that promotes oxidative injury, inflammatory response, mitochondrial dysfunction, and cell death [55, 56].

Over the years, the implications of diabetes on male fertility were trivialized and considered inconsequential by both clinicians and scientists because diabetes was regarded as a late-onset disorder occurring in aged adults. Interestingly, the increasing incidence of diabetes among men of reproductive age has raised serious concerns about reproductive health and fertility outcomes in men [57]. It has been reported that sustained hyperglycemia in men may reduce fertility due to significant injury to sperm DNA causing azoospermia, biochemical and morphological damage to reproductive tissues (epididymis and seminiferous tubules), as well as reduced libido due to low testosterone and other reproductive hormones [58]. Furthermore, studies using male biopsies with diabetes showed anatomical derangement in the testicular capillaries and lymphatics resulting from interstitial matrix accumulation, while disorientation of the Sertoli cell and morphological aberration of the interstitial layer compromising spermatogenesis implies diabetes-induced microvascular complication [59]. Also, an animal paradigm using a streptozotocin-induced diabetic model showed that diabetic rats had significant anatomical and physiological derangement in reproductive function, including reduced seminiferous tubules, empty testicular tubules, and apoptosis [60, 61].

Sexual dysfunctions in males characterized by impotence, retrograde ejaculation, and reduced libido are positively correlated with diabetes and have a significant consequence on male fertility [62]. One major symptom commonly reported by diabetic male patients is ED, which may significantly reduce self-esteem and negatively influence overall reproductive health [63]. Diabetes accounts for about 52.5% incidence of ED, with a higher prevalence in type-II diabetes compared to type-I [40], while the severity of this condition varies with the duration and types, treatment modalities as well as comorbidities [64]. Although, adequate erectile function involves a complex interplay of several factors, including social, endocrine, neural, vascular, and psychological factors. However, diabetes has been implicated in the pathogenesis of ED and is briefly discussed in the subsequent paragraphs.

Persistent hyperglycemia can cause inadequate blood flow to the penis via penile arteries (Fig. 2). In this regard, hyperglycemia increases the deposition of advanced glycated end-products and free radicals within testicular tissues with subsequent oxidative injury and reduced nitric oxide production [65]. Also, hyperglycemia may damage endothelial cells that produce nitric oxide in the penile arteries, compromise guanylyl cyclase activity with reduced cGMP production, and inhibit syncytial relaxation of the erectile muscle [66]. These biochemical processes can inhibit nitric oxide-dependent smooth muscle relaxation thereby reducing blood flow to the penile arteries. Also, it has been reported that endothelin-1 (ET-1) level, a potent vasoconstrictor, is increased in the diabetic serum [67], while endothelin receptors localized on smooth muscle are activated in the erectile muscle in diabetic rabbit [68]. Hence, the increased endothelin and the upregulation of its receptor may contribute to vasoconstriction in the penile arteries, resisting blood flow. Experimental studies showed that the Rho-A/Rho-kinase signal transduction pathway that mediates vasoconstriction is activated in diabetic rats. Activation of this pathway downregulates endothelial nitric oxide synthase (eNOS) and decreases NO production, thereby reducing vasodilation of penile arteries [69, 70].

Furthermore, uncontrolled hyperglycemia can damage the nerve supply to the penis [71], causing poor or no erection [72]. The central nervous system (spinal cord) via the autonomic preganglionic nerve innervates penile erectile muscle to facilitate erection, while the motor neuron via the pudendal nerve enhances penile firmness [30]. Taken together, the spinal nerves modulating erection are influenced by signals from peripheral and supraspinal structures [73]. Thus, adequate penile function, including erection,

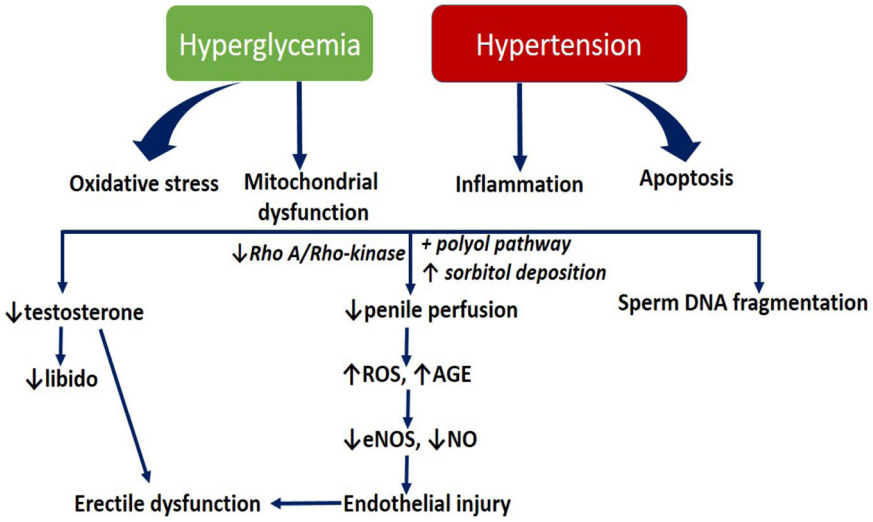

Fig. 2 Schematic illustration of the mechanisms linking diabetes and hypertension with erectile dysfunction. The hyperglycemic state in diabetes and elevated blood pressure seen in hypertension induces oxidative stress, mitochondrial dysfunction, inflammation, and apoptosis, which promotes sperm DNA fragmentation and testicular injury, resulting in impaired testicular steroidogenesis and reduced testosterone production that culminates in impaired libido and erectile dysfunction. Also, oxido-inflammation and mitochondrial dysfunction activates polyol pathways and increases sorbitol deposition, and downregulates Rho A/Rho-kinase, which in turn reduces penile blood flow. This leads to enhanced reactive oxygen species (ROS) generation and advanced glycated end products (AGE), that results in down-regulation of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) and culminates in endothelial injury and erectile dysfunction

relies on optimal nervous control. Notably, some men report erectile complications before proper diagnosis of diabetes, especially type-2 diabetes with poor glycemic control [74, 75]. Notably, nerve dysfunction (neuropathy) has been reported as a major complication in chronic hyperglycemia, and this can be an underlying factor promoting autonomic neuropathy often reported in diabetic impotent males [72]. During diabetes, hyperglycemia activates the polyol pathway, with significant deposition of sorbitol that alters the NAD: NADH ratio and direct injury to the neurons. Also, advanced glycosylated products during hyperglycemia may inhibit blood flow in the endo-neurons, promoting hypoxia that compromises nerve function [76].

Hypertension and ED

Hypertension is a key risk factor for cardiovascular disease (CVD) and a frequent disorder that may share pathophysiologic mechanisms with ED [77]. Hypertensive individuals have a greater rate of ED than the overall population [78]. The question of whether the increased incidence of ED in these individuals is due to hypertension, antihypertensive medication, or both has been highlighted as a crucial caveat [77].

There is a close relationship between the signaling systems involved in the pathophysiology of hypertension and ED since both disorders are associated with an increase in procontractile pathways, which decreases vascular compliance [79] (Fig. 2). There is evidence that elevated AngII levels in the systemic and cavernous circulations of men with ED may play a mechanistic role in the onset of penile detumescence [79, 80]. Since the corpus cavernosum generates and secretes Ang II locally [81], it may play a direct role in hypertension-related ED [82]. In the vasculature and vascular-like structures, prolonged hyperstimulation of the Ang II/AT1r axis is known to induce endothelial dysfunction [83]. Ang II also promotes a robust sympathetic nervous system [84], which, via adrenergic receptors, increases the contractile tone of the arterioles and sinusoidal compartments of the corpus cavernosum [79].

Given that ETA antagonists enhance erectile function in hypertensive animals [85] and that men with ED have significantly higher plasma levels of ET-1 than control subjects [86], it is reasonable to assume that the ET-1/ETA axis may be a clinical target for ED associated with hypertension [79]. This is because endothelial cells, which also produce other endothelium-derived contractile factors, secrete ET-1, a key player in the pathophysiology of human hypertension [87]. This endogenous 21-amino acid peptide not only functions as an autocrine hormone via ETB receptors, but it also has a potent paracrine effect upon stimulation of ETA and ETB receptors in vicinal vascular smooth muscle cells [87].

According to Wu et al. [88], androsterone may also have a role in the processes underlying ED. The connection between aldosterone and ED was made because this hormone stimulates the release of inflammatory cytokines in penile tissue and the generation of ROS in smooth muscle cells via nuclear factor kappa B [89, 90], a transcriptional factor that interacts with ROS [91]. Prior research looked at

the effects of aldosterone on penile contractility since the majority of its effects are mediated via mineralocorticoid receptors, which are found in the human penile corpus cavernosum [92]. It's interesting to note that scientists found that aldosterone enhances the effects of noradrenaline rather than having a direct influence on contraction or relaxation [93]. Aldosterone's involvement in ED linked to hypertension is now becoming clear [79].

In the presence of gaseous transmitters such as hydrogen sulfide (H2S), an endogenous gaseous transmitter [94], and nitric oxide (NO), a protective vasoactive gaseous transmitter with a crucial function in vascular homeostasis [79], both prorelaxation factors, nitric oxide and endothelin, are downregulated in hypertension due to the vascular and vascular-like anatomy of the penis, indicating that these molecules and their downstream pathways may be useful therapeutic targets for both hypertension and ED [79]. Furthermore, since they typically result in an ineffective response, Angiotensin (1,7), a counterregulatory peptide of the renin-angiotensin system with opposite actions to Ang II [95], and Nrf2, which is activated by oxidative stress and, in turn, leads to the expression of antioxidant genes that safeguard against ROS-induced damage to tissues [96], are compromised as well.

According to recent research [97, 98], the immune system is also involved in the etiology of ED and hypertension. Recent studies have demonstrated that the penile function of this organism's innate arm is also impaired [99–103].

ED as a Harbinger of Cardiometabolic Disorders

ED has always been associated with cardiometabolic risk especially in aging individuals as it often precedes the signs and symptoms of cardiovascular disease and cerebrovascular accidents in men and women [104–106]. ED is an independent marker of cardiovascular risk, and an indicator for both obstructive and non-obstructive coronary heart disease [107]. Research evidence favors the understanding that ED is a vascular disorder in most patients as it is associated with diabetes, obesity, depression chronic obstructive pulmonary disease CVD, benign prostatic hypertrophy/lower urinary tract symptoms, hypertension, and dyslipidemia [108]. A supporting finding for this is the increase in the incidence of ED in vascular comorbidities such as hypertension, cerebrovascular disease, atherosclerosis, diabetes, coronary artery disease, and peripheral artery disease [109]. Musicki et al. [105] examined the recent scientific evidence linking ED and cardiometabolic disorders and found that endothelial factors (oxidative stress, and endothelium-derived nitric oxide); smooth muscle (SM) (alteration in the molecular regulation of SM contractility and the abundance of SM); autonomic innervation (decreased neuronal-derived nitric oxide and autonomic neuropathy); metabolic (hyperlipidemia, advanced glycation end product formation and hormones (impaired testosterone release and actions) are culprits linking ED and cardiometabolic disorders. Recent literature explained that there is an update in the older paradigm in which ED was demonstrated to be a sentinel marker for cardiovascular diseases and other comorbidities is directly related to endothelial dysfunction in vascular risk factors [110, 111]. Moreover, cardiometabolic disorders are similar in their pathogenesis of the nitric oxide pathway vasodilation which causes impairment of the endothelial function and structural abnormalities of the vessels [107]. Hence, ED can be considered a harbinger of cardiometabolic risk; a manifestation of the vascular dysfunction that affects blood circulation in the penis. Confirming this found that ED precedes the incidence of cardiovascular disease by 2 to 3 years. Further, there is a growing opinion that ED is a precursor of cardiometabolic disorders and an index subclinical coronary disease via several mechanisms [108]. ED could be a precursor in that it increases cardiac risk due to depression and this together with an increase in body mass index and other comorbidities can lead to cardiometabolic disorders [112]. Using the International Index of Erectile Function-5 items scale, Dursun et al. [112] assessed sexual functions towards a better understanding of the relationship between ED and CMR. The result showed an increase in the CMI levels in the ED group; and because of the simplicity in the measurement of TG and HDL levels, height measurement, and waist circumference, CMI was considered an applicable index for evaluation of cardiovascular dysfunction. Thus, ED is established as a precursor sign for vascular disease and a potential marker for cardiovascular disease, atherosclerosis, and endothelial dysfunction.

Nitric Oxide: A Key Player in the Pathogenesis of ED and Cardiometabolic Disorders

A negative correlation between cardiometabolic disorders and erectile function has been previously established. Decades of research have suggested that the occurrence of cardiometabolic disorders always poses a threat to a lot of body functions including erectile function. Erectile dysfunction is considered one of the conditions that stemmed out in sufferers of cardiometabolic diseases. Beyond estimation of conventional biomarkers that contribute to the development of cardiometabolic diseases, Nitric Oxide (NO), a multifunctional signaling molecule is considered one pivotal biomarker that has been documented in the control of various physiological functions such as mitochondrial homeostasis, energy metabolism, renal homeostasis, vascular regulation among others. Both persistent elevated NO bioavailability and drastic fall in nitric oxide concentrations may contribute to the development of

various diseases such as cancer, cardiovascular dysfunctions, hypertension, metabolic disorders, and vascular dysfunction. Achieving NO homeostasis helps to regulate various physiological pathways in the body including erectile function [13]. NO spreads at the cellular level and activates the guanylate cyclase which in turn increases the production of cyclic guanosine monophosphate and consequently relaxes the cardiac and cavernosal smooth muscle cells [113]. Therefore, NO exerts relaxation of these muscles to achieve physiological events such as arteriolar dilatation, increased blood flow, reduced venous outflow, and finally achieving erection and elevating systolic blood pressure.

Testosterone: For Optimal Erectile Function or Cardiometabolic Function?

A decrease in levels of circulating testosterone is a common factor in ED and cardiometabolic dysfunction. The subject of the involvement of testosterone in a myriad of cardiometabolic diseases has driven many scientific inquiries. Hypogonadism is involved in insulin resistance, atherosclerosis, dyslipidemia, inflammation, and diabetes [114]. Similarly, testosterone replacement therapy improves mood, libido, and muscle strength, and boosts energy levels, and ED [114]. In male physiology, testosterone is required for the release of stimulatory neurotransmitters such as nitric oxide, dopamine, and oxytocin for normal libido, sexual development, mating behaviors, and libido [115]. Testosterone regulates the structure, function of innervation of trabecular smooth muscle cells endothelial function of penile vessels, and the fibroblastic properties of the corpus cavernosum. Testosterone precursor (dihydrotestosterone) and testosterone enhanced improving erectile function by supporting the relaxation of the penile artery and cavernosal smooth muscle [116].

Zitzmann [117] in his review on testosterone deficiency and metabolic syndrome explained that hypogonadism may play a contributory role in the development of the metabolic syndrome and turn, obesity and hyperinsulinemia cause a decrease in biosynthesis of testosterone in the Leydig cells. The relationship has been explained in that hypogonadism may cause an increase in inflammation [118] which disrupts endothelial function, and thus increases the thickness of the arterial wall, vascular stiffening, and ultimately dysfunction [119]. Reports have also suggested that increased testosterone levels may be cardioprotective [119]. In type 2 diabetes, androgen deficiency worsens the increase in carotid intima-media thickness and triggers the mediators of inflammatory response such as tumor necrosis factor (TNF-alpha) and C-reactive protein, which may influence the severity of CAD [115].

However, several clinical trials and observational studies have confirmed that testosterone replacement therapy increases cardiovascular risk with metabolic dysfunction in older men. Findings from Mendelian studies suggest that an increase in the risk of heart failure is associated with genetically predicted increases in testosterone levels. Confirming this, the US Food and Drug Administration cautioned the United States public against treating andropause with testosterone. It was recommended to reserve this type of therapy for symptomatic hypogonadism.

Taken together, testosterone is a common factor in the development of ED and cardiometabolic diseases. It is required for the physiological release of neurotransmitters in male sexual function and regulates the structure and function of penile vessels. In cardiometabolic function, testosterone ensures the normal structure of the arterial wall, inhibits the mediators of the inflammatory response (TNF-alpha) and C-reactive protein, and also prevents vascular stiffening and calcification even though testosterone supplementation may increase cardiovascular risk.

Conclusion and Future Perspectives

Available evidence in the literature revealed that ED may be a cause and/or consequence of cardiometabolic disorders, which are risk factors for cardiovascular diseases. There are compelling pieces of evidence linking ED and cardiometabolic disorders; nonetheless, impairment of nitric oxide-dependent vasodilatation is the primary signaling pathway. Suppression of circulating testosterone increased endothelin-1, and hyperactivation of Ang II/ATIr are also essential key players in the pathogenesis of ED and cardiometabolic disorders. Although there are available strategies employed in the management of cardiometabolic disorders that are useful in preventing incident ED, this study provides a detailed update on the links between cardiometabolic disorders and ED, thus opening a window of opportunities to be explored for potential therapeutic targets in the management of ED and cardiometabolic disorder.

Data Availability

The data used to support the findings of the present study are available from the corresponding author upon request.

Author Contributions Conceptualization and design: D. Adeyemi and R.A. Data curation: D. Adeyemi, D. Arokoyo, M.H., A.D., P.O., and R.A. Funding acquisition: D. Adeyemi, D. Arokoyo, M.H., A.D., P.O., and R.A. Investigation: D. Adeyemi, D. Arokoyo, M.H., A.D., P.O., and R.A. Methodology: D. Adeyemi and R.A. Project administration: D. Adeyemi, D. Arokoyo, M.H., A.D., P.O., and R.A. Supervision: D. Adeyemi and R.A. Validation: R.A. Writing—original draft: D. Adeyemi, D. Arokoyo, M.H., A.D., P.O., and R.A. Writing—review and editing and final approval: D. Adeyemi, D. Arokoyo, M.H., A.D., P.O., and R.A.

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