Erectile Dysfunction as a Clinical Indicator of Endocrine Disorders

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Abstract

Erectile function (EF) is a complex process controlled by a variety of factors, including vascular, neurological, psychological and endocrinological function. There is a complex interrelationship between endocrine health and sexual function, particularly reflecting the importance of testosterone and the contribution of other hormones in EF and the association of hormonal imbalances in the occurrence of erectile dysfunction (ED). Indeed, while wide literature evidence corroborates a strong link between hypogonadism and ED, a consistent association between hyperprolactinemia and ED is highlighted by less numerous studies, and less abundant and consistent studies suggest an association between hypo- and hyperthyroidism, hypo- and hypercortisolism and growth hormone (GH) deficiency and excess on the one hand, and the occurrence of ED, on the other.

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Moreover, the endocrine system modulates EF also by means of its bidirectional relationship with metabolic health; in particular, metabolic syndrome represents a risk factor for hypogonadism, which in turn is associated with an increased prevalence of metabolic disorders and ED. Furthermore, metabolic syndrome directly increases the risk of ED through cardiovascular impairment and endothelial dysfunction. Evidence suggests that the presence of specific hormonal imbalances, such as in testosterone, prolactin and thyroid hormone levels, and of metabolic alterations in patients affected by ED may be of considerable clinical relevance. Accordingly, sexual function and EF should be assessed in patients with hormonal imbalances, particularly patients with hypogonadism and hyperprolactinemia, and with metabolic disorders.

Keywords

Erectile dysfunction · Hypogonadism · Testosterone · Endocrine health · Hormonal imbalances · Metabolic syndrome

6.1 The Interrelationship Between Endocrine Health and Erectile Function

Previous chapters provided a detailed examination of the literature regarding the links between erectile dysfunction (ED) and cardiovascular disease, diabetes mellitus and psychological and lifestyle factors, illustrating the diverse range of influences on erectile function (EF). It is recognised that EF is dependent on a number of processes, including vascular, neurological, psychological and endocrinological function [1]. The current chapter focuses on the role of the endocrine system in the context of sexual health and in the development of ED.

The current section evaluates the literature on the interrelationship between endocrine health and EF, including the importance of testosterone and other hormones, in facilitating EF. The endocrine system is a key regulator for a range of physiological processes and a driver for satisfactory sexual function in humans [2]. The main endocrine contributors to sexual health and EF in men are androgens, including testosterone and, to a relatively lesser extent, dihydrotestosterone (DHT) [3]. However, complex interrelationships among the endocrine axes may impact sexual health and EF through multiple pathways, including testosterone and also the action of other hormones involved in the regulation of stress and vascular, neurological and metabolic functions [2, 4]. Testosterone has a pivotal role in male sexual function, particularly EF [4]. Testosterone is recognised as a physiological driver of male sexual arousal and desire and exerts a permissive action of EF [5]. Studies in animal models demonstrated that the ablation of androgen activity impacts sexual

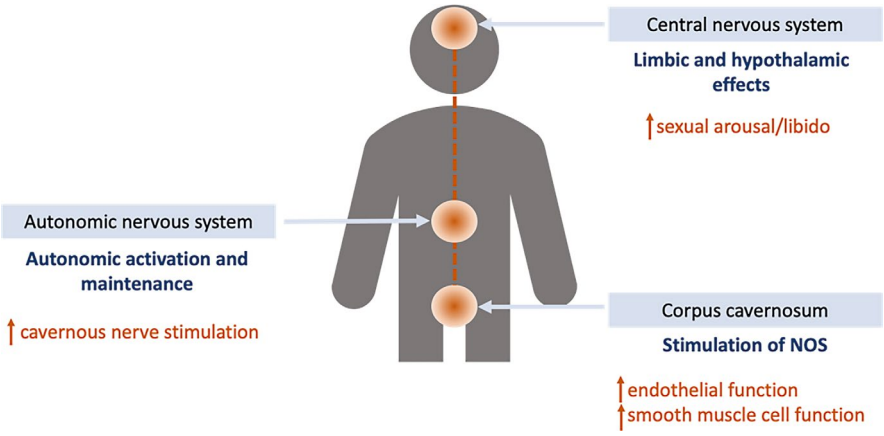

Fig. 6.1 Testosterone actions in the control of sexual response and erectile function. This figure illustrates key targets of androgen/testosterone activity in the central nervous system, the autonomic nervous system and the corpus cavernosum, leading to erection. Abbreviation: *NOS* nitric oxide synthase. (Adapted from [4])

behaviours, whereas human evidence deriving from studies on brain activity in hypogonadal men supports a link between testosterone activity and sexual arousal [6–8].

Testosterone mainly acts at three different sites, namely the brain, spinal neurones and pelvic ganglia, and the penis [3]. For instance, testosterone acts on androgen receptors located in regions of the brain thought to regulate sexual desire, including the mediobasal hypothalamus and the limbic system [8], therefore initiating and sustaining erection. Locally, within the penis, testosterone exerts direct actions on smooth muscle cells by regulating the expression of nitric oxide synthase and increasing the levels of nitric oxide, an important mediator of smooth muscle relaxation, leading to erection and contributing to the timing of erections [9]. Fig. 6.1 summarises the main actions of testosterone in male sexual arousal and EF.

The role of testosterone in regulating sexual response and EF does not provide a complete picture of how endocrine function relates to male sexual health. Indeed, other hormones, such as prolactin, oestradiol (E2), growth hormones (GH), insulin-like growth factor 1 (IGF-1), thyroid hormones, cortisol and oxytocin, play a role in these complex processes, as indirectly highlighted mainly by studies focusing on hormonal excess or deficiency and endocrine pathologies. The direct effects on EF of testosterone, GH and cortisol are summarised in Fig. 6.2.

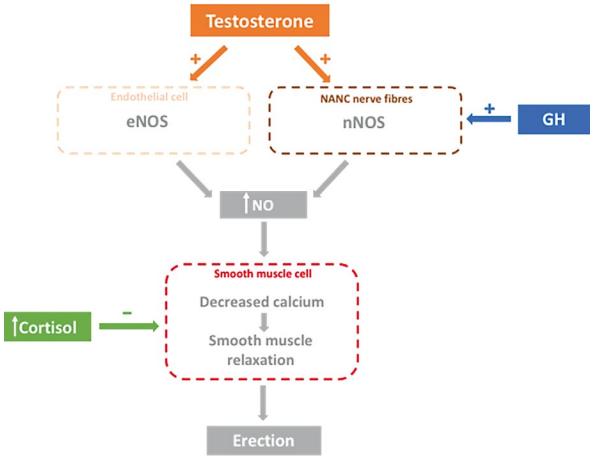

Fig. 6.2 Interrelationship between endocrine axes and erectile function. In smooth muscle cells, nitric oxide (NO) triggers a decrease in calcium levels, mediated by cyclic guanosine monophosphate (cGMP), which causes smooth muscle cell relaxation and subsequently leads to penile erection. Testosterone enhances NO release by stimulating endothelial nitric oxide synthase (eNOS) and noradrenergic noncholinergic (NANC) nerve nitric oxide synthase (nNOS) as well as growth hormone (GH) by stimulating nNOS. High cortisol levels inhibit the decrease in calcium levels, mediated by cyclic adenosine monophosphate (cAMP), therefore interfering with smooth muscle relaxation. (Adapted from reference [10])

6.2 The Association Between Hormonal Imbalances, Endocrine Pathologies and Erectile Dysfunction

One of the key factors supporting a link between endocrine health and EF is the association between hormonal imbalance and ED. Hormonal imbalances have the potential to dramatically modify the endocrinological control of physiological activities, including those linked to sexual behaviours and function. One of the main lines of evidence supporting this association relates to the link between testosterone levels and the risk of ED. For example, a decrease in serum testosterone levels is seen with ageing, during the period in which the prevalence of ED increases [11]. However, this association is complex as some epidemiological studies suggested that the link between ED and testosterone levels may not be linear or significant [12, 13]. Importantly, when testosterone levels fall below the critical threshold value (<8 mmol/L), the association between testosterone and ED is significant [13], therefore suggesting that testosterone levels need to be below a certain threshold (subnormal levels) to cause hypogonadism that is associated with ED.

Further evidence corroborating this hypothesis came from observations that a loss of testosterone activity following castration is associated with a decline in sexual activity and EF [14, 15]. Similarly, a reduction in the amplitude, frequency and rigidity of erections has been demonstrated in men affected by hypogonadism [16]. Accordingly, in hypogonadal men, normal sexual function was restored with

Table 6.1 Summary of associations between low testosterone levels/hypogonadism and erectile dysfunction

Key observations	Supporting study
Men with ED have lower T levels across all phases of EF compared with men without ED.	Becker et al. [40]
Free T levels are associated with increased penile vessel dilation and cavernous artery compliance.	Aversa et al. [41]
The incidence of low libido and reduced EF is higher at T levels below 8 nmol/L.	Zitzmann et al. [42]
Obese men demonstrate lower T and higher rates of ED, independent of obesity-related factors.	Corona et al. [43]
Weight loss in obese hypogonadal men results in an increase in T levels and improvement in EF.	Camacho et al. [44], Rastrelli et al. [45]

Abbreviations: *EF* erectile function, *ED* erectile dysfunction, *T* testosterone

exogenous testosterone treatment [17, 18]. Testosterone treatment in men is generally only associated with an improvement in sexual function where subnormal levels are assessed during endocrinological workup, suggesting that testosterone levels slightly below normal may not be strongly linked to ED and may likely reflect the actions of other risk factors that contribute to ED. A summary of the key observations on the link between testosterone and ED across studies is presented in Table 6.1.

In addition to changes in testosterone levels associated with ageing or pathological conditions, other hormonal imbalances may contribute to compromised EF [19]. For instance, high levels of prolactin have been established as a cause of ED since elevated prolactin negatively modulates the pulsatile hormonal control involved in sexual arousal and EF [20, 21]. Elevation of E2 may lead to the suppression of the hypothalamic-pituitary axis, reducing testosterone levels and potentially affecting EF [22]. Furthermore, thyroid hormone imbalances may be associated with reduced EF, owing to the complex actions of thyroid hormones in regulating mood, sexual arousal and specific effects on the hormonal control of erections [23]. Moreover, associations have been reported between high levels of GH and ED [24] and low levels of IGF-1 and ED [25], while low levels of oxytocin [26] and high levels of cortisol have been associated with ED [27]. These interactions reflect a complex range of pathological conditions and potential mechanisms through which EF may be regulated, emphasising the interrelationship not only between the endocrine regulators of EF but also between the endocrine and other systems, such as inflammation, linked to ED pathophysiology [28]. Indeed, many non-communicable diseases linked to endocrinological status, including diabetes mellitus, metabolic syndrome and obesity, are associated with ED, suggesting common pathogenetic mechanisms, such as inflammation [28]. Elevated inflammatory activity and markers can be seen in these conditions, and these changes have been linked to endothelial dysfunction in blood vessels, a key pathogenic event in the development of ED [29]. Therefore, the diverse nature of the endocrine regulation of ED may be associated with interrelationships between systems as well as key common events in ED pathophysiology, such as inflammation.

Many of the hormonal imbalances observed in association with ED suggest a link between specific endocrine pathologies and ED [30, 31]. For instance, an analysis of patients from the European Male Aging Study found an association between ED and type 2 diabetes mellitus, impaired fasting glucose, hyperprolactinemia and secondary hypogonadism [30]. In particular, male hypogonadism has been reported as the most frequent endocrine alteration affecting ED [9], and the prevalence of ED due to hypogonadism is estimated to be 2–21% [32].

Additionally, epidemiological data linking a diverse range of endocrine conditions with the risk of ED illustrated the importance of hormonal imbalance in normal EF. For example, hyperprolactinemia is associated with the inhibition of gonadotropin-releasing hormone (GnRH), therefore reducing gonadotropin and testosterone secretion, and may be linked to ED in 2% of cases [33]. Thyroid dysfunction has been associated with ED in some studies, reflecting the link between both hypo- and hyperthyroidism and sexual and erectile functions [34, 35]. GH deficiency and acromegaly have also been associated with ED [36, 37]. Furthermore, hypo- and hypercortisolism have likewise been linked to ED in some studies [38, 39].

6.3 The Association Between Metabolic Syndrome and Erectile Dysfunction

Metabolic syndrome is a clinical condition characterised by the presence of at least three metabolic abnormalities, such as increased waist circumference, elevated triglyceride levels, reduced high-density lipoprotein cholesterol levels, elevated fasting glucose and hypertension (Table 6.2), and is linked to a significant increase in 5- and 10-year cardiovascular risk [46, 47]. The condition is closely linked to obesity and insulin resistance, which may contribute to hormonal imbalance in patients affected by metabolic syndrome [48]. In particular, from the perspective of sexual health, metabolic syndrome may be associated with low testosterone levels in a picture of hypogonadotropic hypogonadism [48, 49]. Hypogonadotropic hypogonadism has been linked to the development and exacerbation of metabolic disorders,

Table 6.2 Overview of the main components of metabolic syndrome and their pathophysiological link to erectile dysfunction

Metabolic syndrome criteria	Pathophysiological link with ED increased risk
Elevated waist circumference	Anthropometric features linked to adiposity and abdominal obesity are associated with inflammation and endothelial dysfunction
Elevated triglycerides	Increased risk of atherosclerosis
Low HDL-cholesterol	HDL-cholesterol promotes lipid metabolism and transport, and its low levels reduce protection against atherosclerosis
Elevated blood pressure	Increased endothelial dysfunction
Elevated fasting blood glucose	Insulin resistance leading to endothelial dysfunction

Abbreviations: *ED* erectile dysfunction, *HDL* high-density lipoprotein cholesterol [55]

such as metabolic syndrome, through a number of mechanisms, including an increase in visceral adiposity and the development of insulin resistance [49]. Metabolic disorders further contribute to worsening testosterone deficiency, providing a bidirectional causal relationship between testosterone and metabolic disruption in functional hypogonadotropic hypogonadism [49]. Associations between hypogonadism and metabolic syndrome have been seen in epidemiological data. For instance, systematic reviews of studies have found that men with metabolic syndrome have lower testosterone levels in cross-sectional data, with hypogonadism being more common in men with ED compared to those without ED, while longitudinal data support a bidirectional relationship where low testosterone increases the risk of subsequent metabolic syndrome and vice versa [50, 51].

Importantly, metabolic syndrome is linked to an increased risk of ED [48, 52]. This association has been observed in data elucidating the link between ED and cardiovascular health, as discussed in detail in Chap. 2. Specifically, the risk of ED is increased in patients with cardiovascular disease as well as in those with cardiovascular risk factors [53]. It has been observed that the onset of ED may precede the development of cardiovascular disease by years in patients with cardiovascular risk factors, such as hypertension, smoking and dyslipidaemia, highlighting the role of ED as an early predictor of cardiovascular disease [54]. This has been particularly noted in patients with metabolic syndrome, where a constellation of cardiovascular risk factors is present [53].

A number of studies have investigated the link between metabolic syndrome and ED, supporting an association between metabolic disease and compromised EF. Specifically, a study of 268 men found that those with metabolic syndrome (n = 89) were more likely to have ED according to International Index of Erectile Function (IIEF) scores, with 74% reporting ED compared with 50% of those without metabolic syndrome [55]. Similarly, in another study, it was shown that, in men aged over 50 years, the presence of the metabolic syndrome is associated with an increased risk of moderate or severe ED based on IIEF-5 score [56]. Furthermore, in patients attending urology outpatient clinics (n = 393) aged 40–70 years, there was a significant association between metabolic syndrome and ED [57].

It has been established that there is a link between the severity of metabolic syndrome and the severity of ED in affected individuals [58]. In this context, an observational study found that the number of metabolic syndrome components increased with the severity of ED, with moderate or severe ED associated with the highest risk of metabolic syndrome [59]. Similarly, the EF domain score of the IIEF questionnaire significantly decreased as the number of metabolic risk factors increased in men with metabolic syndrome and patients with the risk factor of elevated fasting blood glucose and waist circumference, or hypertension had lower EF domain scores than patients with other metabolic risk factors [55]. Together, these findings illustrate how cardiovascular and metabolic risk factors have strong associations with ED in middle-aged and older male populations, with the number of metabolic syndrome risk factors linked to the severity of ED. As illustrated in Table 6.2, the main components of metabolic syndrome may be associated specifically with the pathological aspects of ED, accounting for these findings.

6.4 The Potential of Early Erectile Dysfunction Presentation to Trigger Investigations for Endocrine and Metabolic Pathologies

As discussed in the previous chapter in relation to cardiovascular disease, the potential for ED to serve as an early marker of poor health may be an important concept in endocrine and metabolic health contexts, relying upon the vulnerability of EF to hormonal imbalances and dysregulation compared with other physiological functions [60]. The importance of screening for endocrine and metabolic disorders in ED lies not only in their common association with ED but also in how modifiable these conditions are, providing an opportunity for profound improvement in both ED and broader patient health (Fig. 6.3) [60]. Indeed, different studies highlighted the important overlap between ED and undiagnosed endocrine and metabolic disorders. For instance, in an Italian cohort study of 1332 men referred for ED during 2013–2020, 19% were already receiving treatment for pre-diabetes, diabetes or other endocrine dysfunctions, and 30% of the remaining population had previously undiagnosed endocrine or metabolic pathologies, including hypogonadism (58.8%), hyperprolactinemia (11.5%), thyroid dysfunction (12.3%) and metabolic disorders such as glycaemic disorders (17.3%) [60]. Another study also showed that men with sub-clinical hyperthyroidism were more likely to have ED than men with euthyroidism, suggesting that the link between ED and endocrinological dysfunction may be present prior to overt clinical symptoms or the diagnosis of clear endocrine disorders [61]. However, data remain limited regarding the presence of undiagnosed or sub-clinical endocrinological conditions in men with ED, and longitudinal data supporting a temporal relationship are also lacking. Meanwhile, some data suggest a clearer role in the potential discovery of undiagnosed metabolic conditions, such as type 2 diabetes mellitus, in men affected by ED [62]. However, this concept should be interpreted cautiously as hormonal imbalances could play a role in type 2 diabetes development, but other cardiovascular risk factors could also contribute to the development of this condition, complicating how ED may be used as a specific marker for endocrine or metabolic conditions.

It is important to consider the clinical significance and implications of the association between established ED and endocrine pathologies at a population level. Evidence of the value of screening for endocrine pathologies in patients with ED suggested that metabolic and endocrine assessments should be consistently implemented in men with ED [60]. Indeed, tools and strategies have been developed to facilitate endocrinological assessment in men with ED. For example, the ANDROTEST is a structured interview developed and validated for the screening of hypogonadism in men with sexual dysfunction [63], and it holds potential value in clinical practice [63, 64]. Screening results of over 1000 men with ED to determine testosterone deficiency suggested that routine screening in men aged over 50 years is justified [65]. However, some doubts still remain about the opportunity of screening for testosterone levels specifically in men with ED due to uncertainties over specific values on their real indicative or supportive role of sexual dysfunction;

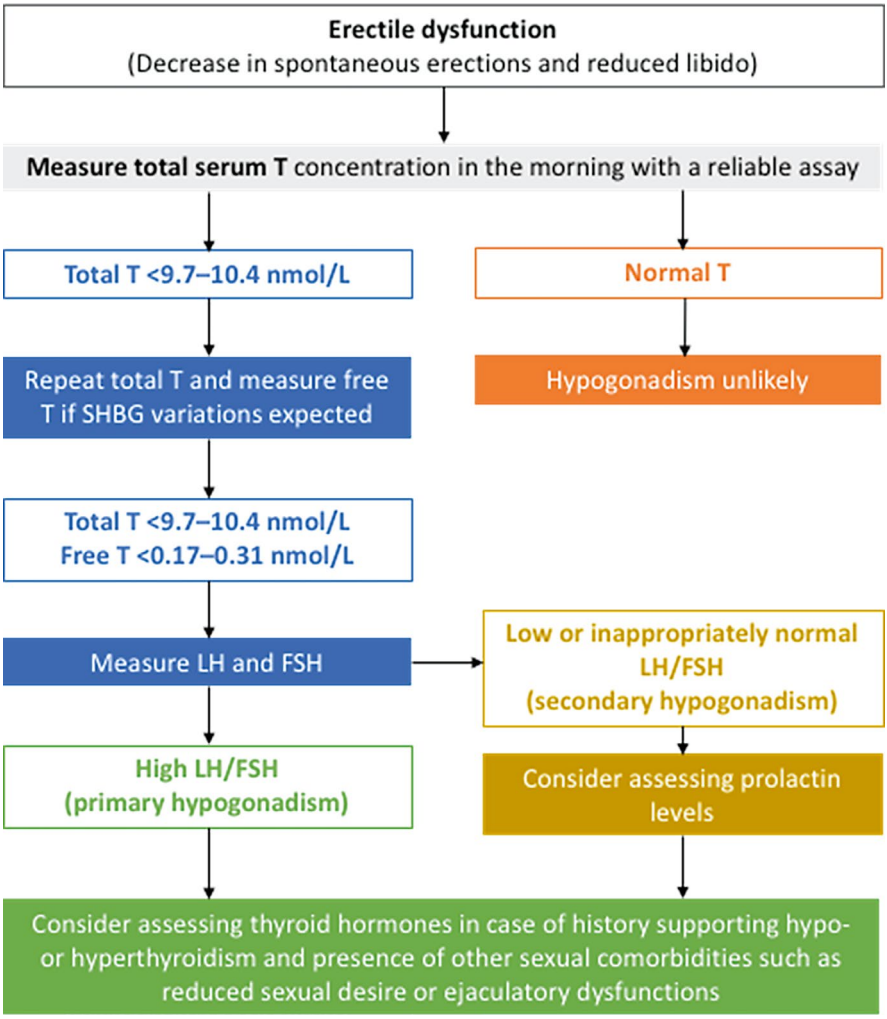

Fig. 6.3 Diagram of a potential screening approach for endocrine pathologies (ED) in patients presenting with erectile dysfunction. The approach to endocrinological assessment of the patient presenting with ED should focus on the initial assessment of testosterone (T), the results of which then guide the need for further endocrinological assessments. Abbreviations: *ED* erectile dysfunction, *FSH* follicle-stimulating hormone, *LH* luteinising hormone, *SHBG* sex-hormone-binding globulin, *T* testosterone. (Adapted from reference [70])

indeed, such screening approaches are not still widely considered feasible due to a lack of consensus on lower limits of testosterone serum levels [66].

Prolactin levels may be eligible for screening in patients with suspected endocrinological causes of ED [48]. It has been suggested that the most effective and cost-effective way of incorporating prolactin screening in patients with ED would involve initial screening for testosterone levels in order to assess evidence of secondary

hypogonadism, followed by prolactin screening [65]. However, this stepwise approach has recently been discussed based on a lack of cost-effectiveness [67], which warrants further consideration. Support for caution in endocrinological screening in patients affected by ED is evident in the wider literature, reflecting a paucity of high-quality studies evaluating screening strategies and outcomes. In this context, screening approaches for hormones should not be considered independently from clinical history, signs and symptoms that may support a diagnosis of endocrine disease. For instance, universal screening for thyroid dysfunction in patients with ED may not be cost-effective but may be of value when combined with detailed history supporting hypo- or hyperthyroidism and other sexual comorbidities, such as reduced sexual desire or ejaculatory dysfunctions [47, 66]. Universal screening for other hormonal imbalances, such as cortisol, GH/IGF-1 and E2, in patients with ED is not widely recommended at present [47]. Therefore, the presence of ED should trigger an exploration of potential selected hormonal imbalances, but there is a need to refine strategies to maximise the clinical value and cost-effectiveness of screening approaches.

Metabolic screening in patients with ED should be considered appropriate in clinical practice due to the strong association between ED and metabolic conditions, such as type 2 diabetes mellitus and metabolic syndrome [47]. Screening for type 2 diabetes mellitus and/or glycaemic disorders is straightforward in practice and therefore may easily be integrated into routine patient evaluation [47]. A diagnosis of ED may have the potential to enhance evaluation for type 2 diabetes mellitus using standardised screening approaches [68]. Wider assessments for cardiovascular and metabolic risk factors are advocated in men presenting with ED as part of an initial workup [47, 69], which may ultimately support the identification or diagnosis of other metabolic conditions.

6.5 Evaluation of Erectile Dysfunction as an Integrated Part of Endocrinological Assessments

Considering that ED is known to be associated with hormonal imbalances and endocrine pathologies, there is wide justification for the evaluation of ED in male patients with endocrine conditions, including hypogonadism, hyperprolactinemia, thyroid disorders and other conditions. A recent consensus statement from the Italian Society of Andrology and Sexual Medicine (SIAMS) and ten other Italian scientific societies [47] recommends considering sexual function investigation in patients with endocrine disorders, including thyroid, adrenal and pituitary diseases. Therefore, integrating the evaluation of sexual function and ED into endocrinological assessments represents an important stage in optimising the identification and initiation of management for ED.

In the presence of endocrine or metabolic disorders, particularly if these conditions could be associated with hypogonadism, the exploration of sexual function should be recommended [71]. SIAMS consensus recommended incorporating EF evaluation for all patients with diabetes mellitus, given that ED is strongly

associated with diabetes duration, metabolic control and the coexistence of diabetic complications [47]. Moreover, an investigation of EF should always be performed in the case of male hypogonadism and hyperprolactinemia and is suggested in the case of clinically manifest hypo- and hyperthyroidism, hypo- and hypercortisolism and GH deficiency and excess [47].

The strategies used to identify ED should rely on clinical assessment/anamnesis, as well as the use of formal tools, such as IIEF/IIEF-5 questionnaires [72]. There is a recognised need for biomarkers that may be indicative of ED, not only to assist in the recognition of the condition but also to inform future risk of ED and the progression of disease in those patients with endocrine disorders [73]. Therefore, the identification of serum biomarkers may have particular value in elucidating ED risk and in facilitating interventions in patients with endocrine and metabolic disorders.

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References

1. Goldstein I, Burnett AL, Rosen RC, Park PW, Stecher VJ. The serendipitous story of sildenafil: an unexpected oral therapy for erectile dysfunction. Sex Med Rev. 2019;7(1):115–28.
2. Corona G, Isidori AM, Aversa A, Burnett AL, Maggi M. Endocrinologic control of men's sexual desire and arousal/erection. J Sex Med. 2016;13(3):317–37.
3. Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. Eur Urol. 2014;65(1):99–112.
4. Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, et al. Erectile dysfunction. Nat Rev Dis Primers. 2016;2:16003.
5. Nguyen V, Leonard A, Hsieh T-C. Testosterone and sexual desire: a review of the evidence. Androg Clin Res Ther. 2022;3(1):85–90.
6. Arteaga-Silva M, Vigueras-Villaseñor RM, Retana-Márquez S, Hernández-González M, Chihuahua-Serrano C, Bonilla-Jaime H, et al. Testosterone, androstenedione, and 5alpha-dihydrotestosterone on male sexual behavior and penile spines in the hamster. Physiol Behav. 2008;94(3):412–21.
7. Mazzola CR, Mulhall JP. Impact of androgen deprivation therapy on sexual function. Asian J Androl. 2012;14(2):198–203.
8. Hauger RL, Saelzler UG, Pagadala MS, Panizzon MS. The role of testosterone, the androgen receptor, and hypothalamic-pituitary-gonadal axis in depression in ageing men. Rev Endocr Metab Disord. 2022;23(6):1259–73.
9. Mazzilli F. Erectile dysfunction: causes, diagnosis and treatment: an update. JCM. 2022;11(21):6429.
10. Salvio G, Martino M, Giancola G, Arnaldi G, Balercia G. Hypothalamic-pituitary diseases and erectile dysfunction. J Clin Med. 2021;10(12)
11. Morley JE, Kaiser FE, Perry HM, Patrick P, Morley PM, Stauber PM, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metab Clin Exp. 1997;46(4):410–3.
12. Kupelian V, Shabsigh R, Travison TG, Page ST, Araujo AB, McKinlay JB. Is there a relationship between sex hormones and erectile dysfunction? Results from the Massachusetts male aging study. J Urol. 2006;176(6 Pt 1):2584–8.

13. O'Connor DB, Lee DM, Corona G, Forti G, Tajar A, O'Neill TW, et al. The relationships between sex hormones and sexual function in middle-aged and older European men. J Clin Endocrinol Metab. 2011;96(10):E1577–87.
14. Rousseau L, Dupont A, Labrie F, Couture M. Sexuality changes in prostate cancer patients receiving antihormonal therapy combining the antiandrogen flutamide with medical (LHRH agonist) or surgical castration. Arch Sex Behav. 1988;17(1):87–98.
15. Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ. Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. J Clin Endocrinol Metab. 1994;78(3):711–6.
16. Guay AT. Testosterone and erectile physiology. Aging Male. 2006;9(4):201–6.
17. Davidson JM, Camargo CA, Smith ER. Effects of androgen on sexual behavior in hypogonadal men. J Clin Endocrinol Metab. 1979;48(6):955–8.
18. Morales A, Johnston B, Heaton JP, Lundie M. Testosterone supplementation for hypogonadal impotence: assessment of biochemical measures and therapeutic outcomes. J Urol. 1997;157(3):849–54.
19. De Rocco PM, Selice R, Di Mambro A, De Toni L, Foresta C, Garolla A. Estradiol-testosterone imbalance is associated with erectile dysfunction in patients with Klinefelter syndrome. J Clin Med. 2021;10(11)
20. Doherty PC, Baum MJ, Todd RB. Effects of chronic hyperprolactinemia on sexual arousal and erectile function in male rats. Neuroendocrinology. 1986;42(5):368–75.
21. Xu Z-H, Pan D, Liu T-Y, Yuan M-Z, Zhang J-Y, Jiang S, et al. Effect of prolactin on penile erection: a cross-sectional study. Asian J Androl. 2019;21(6):587–91.
22. Chen H-R, Tian R-H, Li P, Chen H-X, Xia S-J, Li Z. Estradiol is an independent risk factor for organic erectile dysfunction in eugonadal young men. Asian J Androl. 2020;22(6):636–41.
23. Bates JN, Kohn TP, Pastuszak AW. Effect of thyroid hormone derangements on sexual function in men and women. Sex Med Rev. 2020;8(2):217–30.
24. Chen Z, Shao X, He M, Shen M, Gong W, Wang M, et al. Erectile dysfunction is associated with excessive growth hormone levels in male patients with acromegaly. Front Endocrinol (Lausanne). 2021;12:633904.
25. Otunctemur A, Ozbek E, Sahin S, Ozcan L, Dursun M, Polat EC, et al. Low serum insulin-like growth factor-1 in patients with erectile dysfunction. Basic Clin Androl. 2016;26:1.
26. Melis MR, Argiolas A. Oxytocin, erectile function and sexual behavior: last discoveries and possible advances. Int J Mol Sci. 2021;22(19)
27. Rahardjo HE, Becker AJ, Märker V, Kuczyk MA, Ückert S. Is cortisol an endogenous mediator of erectile dysfunction in the adult male? Transl Androl Urol. 2023;12(5):684–9.
28. Jannini EA. SM = SM: the interface of systems medicine and sexual medicine for facing non-communicable diseases in a gender-dependent manner. Sex Med Rev. 2017;5(3):349–64.
29. Roumeguère T, Van Antwerpen P, Fathi H, Rousseau A, Vanhamme L, Franck T, et al. Relationship between oxidative stress and erectile function. Free Radic Res. 2017;51(11–12):924–31.
30. Maseroli E, Corona G, Rastrelli G, Lotti F, Cipriani S, Forti G, et al. Prevalence of endocrine and metabolic disorders in subjects with erectile dysfunction: a comparative study. J Sex Med. 2015;12(4):956–65.
31. Maggi M, Buvat J, Corona G, Guay A, Torres LO. Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). J Sex Med. 2013;10(3):661–77.
32. Corona G, Lee DM, Forti G, O'Connor DB, Maggi M, O'Neill TW, et al. Age-related changes in general and sexual health in middle-aged and older men: results from the European male ageing study (EMAS). J Sex Med. 2010;7(4 Pt 1):1362–80.
33. Corona G, Rastrelli G, Bianchi N, Sparano C, Sforza A, Vignozzi L, et al. Hyperprolactinemia and male sexual function: focus on erectile dysfunction and sexual desire. Int J Impot Res. 2024;36(4):324–32.
34. Gabrielson AT, Sartor RA, Hellstrom WJG. The impact of thyroid disease on sexual dysfunction in men and women. Sex Med Rev. 2019;7(1):57–70.

35. Liu X, Wang Y, Ma L, Wang D, Peng Z, Mao Z. High prevalence of erectile dysfunction in men with hyperthyroidism: a meta-analysis. BMC Endocr Disord. 2024;24(1):58.
36. Lotti F, Rochira V, Pivonello R, Santi D, Galdiero M, Maseroli E, et al. Erectile dysfunction is common among men with acromegaly and is associated with morbidities related to the disease. J Sex Med. 2015;12(5):1184–93.
37. Pivonello R, Auriemma RS, Delli Veneri A, Dassie F, Lorusso R, Ragonese M, et al. Global psychological assessment with the evaluation of life and sleep quality and sexual and cognitive function in a large number of patients with acromegaly: a cross-sectional study. Eur J Endocrinol. 2022;187(6):823–45.
38. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol. 2016;4(7):611–29.
39. Granata A, Tirabassi G, Pugni V, Arnaldi G, Boscaro M, Carani C, et al. Sexual dysfunctions in men affected by autoimmune Addison's disease before and after short-term gluco- and mineralocorticoid replacement therapy. J Sex Med. 2013;10(8):2036–43.
40. Becker AJ, Ückert S, Stief CG, Scheller F, Knapp WH, Hartmann U, et al. Cavernous and systemic testosterone plasma levels during different penile conditions in healthy males and patients with erectile dysfunction. Urology. 2001;58(3):435–40.
41. Aversa A, Isidori AM, De Martino MU, Caprio M, Fabbrini E, Rocchietti-March M, et al. Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. Clin Endocrinol. 2000;53(4):517–22.
42. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006;91(11):4335–43.
43. Corona G, Mannucci E, Fisher AD, Lotti F, Petrone L, Balercia G, et al. Low levels of androgens in men with erectile dysfunction and obesity. J Sex Med. 2008;5(10):2454–63.
44. Camacho EM, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, et al. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European male ageing study. Eur J Endocrinol. 2013;168(3):445–55.
45. Rastrelli G, Carter EL, Ahern T, Finn JD, Antonio L, O'Neill TW, et al. Development of and recovery from secondary hypogonadism in aging men: prospective results from the EMAS. J Clin Endocrinol Metab. 2015;100(8):3172–82.
46. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; world heart federation; international atherosclerosis society; and International Association for the Study of obesity. Circulation. 2009;120(16):1640–5.
47. Corona G, Cucinotta D, Di Lorenzo G, Ferlin A, Giagulli VA, Gnessi L, et al. The Italian Society of Andrology and Sexual Medicine (SIAMS), along with ten other Italian scientific societies, guidelines on the diagnosis and management of erectile dysfunction. J Endocrinol Investig. 2023;46(6):1241–74.
48. Corona DG, Vena W, Pizzocaro A, Rastrelli G, Sparano C, Sforza A, et al. Metabolic syndrome and erectile dysfunction: a systematic review and meta-analysis study. J Endocrinol Investig. 2023;46(11):2195–211.
49. Pivonello R, Menafra D, Riccio E, Garifalos F, Mazzella M, de Angelis C, et al. Metabolic disorders and male hypogonadotropic hypogonadism. Front Endocrinol (Lausanne). 2019;10:345.
50. Corona G, Rastrelli G, Morelli A, Vignozzi L, Mannucci E, Maggi M. Hypogonadism and metabolic syndrome. J Endocrinol Investig. 2011;34(7):557–67.
51. Dimopoulou C, Goulis DG, Corona G, Maggi M. The complex association between metabolic syndrome and male hypogonadism. Metab Clin Exp. 2018;86:61–8.
52. Corona G, Rastrelli G, Filippi S, Vignozzi L, Mannucci E, Maggi M. Erectile dysfunction and central obesity: an Italian perspective. Asian J Androl. 2014;16(4):581–91.
53. Corona G, Rastrelli G, Isidori AM, Pivonello R, Bettocchi C, Reisman Y, et al. Erectile dysfunction and cardiovascular risk: a review of current findings. Expert Rev Cardiovasc Ther. 2020;18(3):155–64.

54. Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol. 2003;44(3):360–4.
55. Demir T, Demir O, Kefi A, Comlekci A, Yesil S, Esen A. Prevalence of erectile dysfunction in patients with metabolic syndrome. Int J Urol. 2006;13(4):385–8.
56. Heidler S, Temml C, Broessner C, Mock K, Rauchenwald M, Madersbacher S, et al. Is the metabolic syndrome an independent risk factor for erectile dysfunction? J Urol. 2007;177(2):651–4.
57. Bal K, Oder M, Sahin AS, Karataş CT, Demir O, Can E, et al. Prevalence of metabolic syndrome and its association with erectile dysfunction among urologic patients: metabolic backgrounds of erectile dysfunction. Urology. 2007;69(2):356–60.
58. Sanchez E, Pastuszak AW, Khera M. Erectile dysfunction, metabolic syndrome, and cardiovascular risks: facts and controversies. Transl Androl Urol. 2017;6(1):28–36.
59. García-Cruz E, Leibar-Tamayo A, Romero J, Piqueras M, Luque P, Cardeñosa O, et al. Metabolic syndrome in men with low testosterone levels: relationship with cardiovascular risk factors and comorbidities and with erectile dysfunction. J Sex Med. 2013;10(10):2529–38.
60. Mazzilli R, Zamponi V, Olana S, Mikovic N, Cimadomo D, Defeudis G, et al. Erectile dysfunction as a marker of endocrine and glycemic disorders. J Endocrinol Investig. 2022;45(8):1527–34.
61. Chen D, Yan Y, Huang H, Dong Q, Tian H. The association between subclinical hypothyroidism and erectile dysfunction. Pak J Med Sci Q. 2018;34(3):621–5.
62. Tucker J, Salas J, Secrest S, Scherrer JF. Erectile dysfunction associated with undiagnosed prediabetes and type 2 diabetes in young adult males: a retrospective cohort study. Prev Med. 2023;174:107646.
63. Corona G, Mannucci E, Petrone L, Balercia G, Fisher AD, Chiarini V, et al. ANDROTEST: a structured interview for the screening of hypogonadism in patients with sexual dysfunction. J Sex Med. 2006;3(4):706–15.
64. Millar AC, Lau ANC, Tomlinson G, Kraguljac A, Simel DL, Detsky AS, et al. Predicting low testosterone in aging men: a systematic review. CMAJ. 2016;188(13):E321–30.
65. Buvat J, Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. J Urol. 1997;158(5):1764–7.
66. Sansone A, Romanelli F, Gianfrilli D, Lenzi A. Endocrine evaluation of erectile dysfunction. Endocrine. 2014;46(3):423–30.
67. Morgado A, Moura ML, Dinis P, Silva CM. Current stepwise recommendations for hypogonadism screening in erectile dysfunction are not cost-effective. Int J Impot Res. 2020;32(3):297–301.
68. Carrillo-Larco RM, Luza-Dueñas AC, Urdániga-Hung M, Bernabé-Ortiz A. Diagnosis of erectile dysfunction can be used to improve screening for type 2 diabetes mellitus. Diabet Med. 2018;35(11):1538–43.
69. Meng X, Rao K, Chen J. Editorial: metabolic factors in erectile dysfunction. Front Endocrinol (Lausanne). 2023;14
70. Basaria S. Male hypogonadism. Lancet. 2014;383(9924):1250–63.
71. Bhasin S, Enzlin P, Coviello A, Basson R. Sexual dysfunction in men and women with endocrine disorders. Lancet. 2007;369(9561):597–611.
72. Goyal A, Singh P, Ahuja A. Prevalence and severity of erectile dysfunction as assessed by IIEF-5 in north Indian type 2 diabetic males and its correlation with variables. J Clin Diagn Res. 2013;7(12):2936–8.
73. Patel DP, Craig JR, Myers JB, Brant WO, Hotaling JM. Serum biomarkers of erectile dysfunction in diabetes mellitus: a systematic review of current literature. Sex Med Rev. 2017;5(3):339–48.