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# The Canary in the Coalmine

## Erectile Dysfunction as the Best Biomarker of Non-Communicable Chronic Diseases

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# The Canary in the Coalmine

## Erectile Dysfunction as the Best Biomarker of Non-Communicable Chronic Diseases

Springer

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# Contents

# The Canary and the Bone: A Darwinian Lecture on Erectile Dysfunction

1

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**Abstract**

Erectile dysfunction (ED) is one of the most common impairments in sexual function seen in males. The pathogenesis of ED is commonly attributed to a complex interaction of biological, psychological and social factors. The high prevalence of ED and its impact on male sexual function require further explanation from an evolutionary perspective, as one might expect the forces of natural selection to reduce ED frequency over generations. This chapter explores the Darwinian perspective of ED and highlights the importance of sexual selection

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and the loss of the penile bone, the *baculum*, as contributing to the presence and persistence of ED in human males. This chapter unravels the complexity of the evolutionary basis of ED, examining the hypothesis that the loss of baculum has generated ED, which serves, like the *canary in the coalmine*, as an early marker of general health. Thus, the inability to achieve and/or maintain an erection adequate for the fulfillment of sexual intercourse might act as a "fuse" for species preservation. Similarly to how fuses burn in a car to prevent more extensive damage, ED would develop in men who harbor other concurrent conditions, or exposed to accumulation of several risk factors of various origin, as a measure to prevent "damage" to the species as a whole. This mechanism would favor reproduction of healthier men, while at the same time reducing the risk of transmission of harmful genes to subsequent generations. The implications of this hypothesis are explored, as well as the importance of modern medicines targeting the phosphodiesterase 5 enzyme in overcoming the evolutionary handicap of ED.

**Keywords**
Erectile dysfunction · Evolution · Darwin · Baculum · Systems sexology · Handicap, PDE5i

## 1.1 Introduction: Dissecting Erectile Failures

**Erectile dysfunction** (ED) is defined as the *recurrent and persistent inability to achieve or maintain an erection firm enough for satisfactory sexual intercourse* in the presence of proper erotic stimuli [1]. According to the recent Italian Society of Andrology and Sexual Medicine (SIAMS) guidelines on ED, the condition may be classified based on the severity of symptoms (subclinical, mild, moderate, and severe) [2]. **Subclinical ED** (SED), identified through strict and well-defined major and minor criteria, is the pathological burden of men who are not affected by 'clinical' ED but experience inconsistent, situation-, partner-, and mood-related difficulties with erection or reduced penile hardness, which can inconstantly interfere with penetration [3]. When these definitions are considered, the prevalence of ED and SED is high among the male population. Analyses of the global epidemiology of ED show that the condition is prevalent across countries [4, 5]. While SED has been recently observed in 4.4% of 11,200 patients attending an outpatient andrological centre [6], the overall estimated prevalence of ED varies considerably, depending on the study and the methods used to define ED and to measure this phenomenon, with estimates ranging from 3% to 76.5% [7]. A summary of the prevalence of ED across nations is presented in Table 1.1.

It is thought that cases of ED are increasing over time, reflecting a growing burden of the condition in modern society [9]. Incidence increases have been noted in the literature, particularly in recent decades, which may reflect changes in the recognition of ED following the introduction of successful pharmacological options to manage this condition in the late 1990s [10]. Rising ED rates may reflect a genuine growth in male sexual dysfunction cases over time, as well as increased public

**Table 1.1** Prevalence of ED across eight nations in men aged 18 years or older and 40–70 years of age [8]

| Nation | Population | Prevalence of ED (%) |
|---|---|---|
| Brazil | ≥18 years<br>40–70 years | 37.2<br>42.1 |
| China | ≥18 years<br>40–70 years | 41.6<br>47.4 |
| France | ≥18 years<br>40–70 years | 44.9<br>47.8 |
| Germany | ≥18 years<br>40–70 years | 44.9<br>46.1 |
| Italy | ≥18 years<br>40–70 years | 48.6<br>52.2 |
| United Kingdom | ≥18 years<br>40–70 years | 42.6<br>42.6 |
| United States | ≥18 years<br>40–70 years | 42.0<br>46.1 |

awareness of these issues [9]. However, the global burden (i.e. the total number of patients with SED and ED) is expected to increase considerably with time due to the ageing population and the rise in the rates of ED seen across nations, where population growth and lifestyle factors linked to ED are notable, such as in China [11].

One of the key trends in the prevalence of ED is its association with age [12], with a considerable increase in men older than 40 years. The Massachusetts Male Aging Study [13] found that the self-reported prevalence of ED in men aged 40–70 years was 52% (17.2% mild, 25.2% moderate and 9.6% severe), while within this age group, there was a threefold increase in prevalence between men aged 40 and 70 years. A follow-up in this population over an average of 8.8 years found that the annual incidence of ED increased by decade, with 12.4 cases per 1000 man-years in those aged 40–49 years, 29.8 for men aged 50–59 years and 46.4 for men aged 60–69 years [14]. Another large survey conducted in a German cohort of 8000 men aged 30–80 years reported an overall prevalence of ED at 19.2%, increasing from 2.3% at 30 years of age to 53.4% at 80 years of age [15]. These findings are supported by more recent data on the association between age and ED [16, 17].

It is important to consider that the prevalence of ED may be underestimated in available literature due to factors such as male privacy, reluctance to discuss the condition or social and cultural beliefs influencing attitudes towards sexual function and behaviour [4]. In addition, while age is strongly associated with ED, the condition also occurs in younger age groups of men [18]. Although not demonstrated yet, SED could be expected to more typically affect young populations, being a bona fide prodromic stage of clinical ED [3]. Hence, while age is likely to have an important influence on erectile function, one must consider that with increasing age, there is also a higher likelihood of health risk factors, chronic conditions and comorbidities that may influence the potential for ED, which may also be present in a smaller proportion of younger men [4, 16]. Indeed, it has been noted that the risk of ED sharply increases with the accumulation of comorbidities [16]. The risk factors underlying SED and ED will be considered later in this chapter.

Due to the high prevalence of ED, this condition is one of the most commonly managed impairments of sexual function in clinical practice. Indeed, the impact of ED on sexual performance is widely recognised [19]. Erectile function is essential for successful copulation, and the development of ED may lead to poor sexual performance [20]. In addition, ED can have profound effects beyond its biological impact on sexual performance, influencing psychological health, social well-being and other important outcomes from a holistic care perspective [21]. Indeed, it has been noted that patients with ED experience a greater burden of psychological and relational symptoms than the healthy population, along with lower health-related quality of life and impairments in daily activities and occupational function [21]. These consequences are noted in Fig. 1.1. Men with ED need treatment approaches that take into account their personal experiences and preferences [22]. Hence, it is important that this highly prevalent condition, which is associated with a range of challenges and needs, should be considered a key focus of sexual medicine.

## 1.2 Erectile Dysfunction from the Bio-Psycho-Social Model to the Systems Sexology and the Darwinian Perspective

To better understand the major clinical aspects of ED, a new concept needs to be introduced to amplify and extend the well-known bio-psycho-social (BPS) model [24] into a more complex one we call *systems sexology* (SS), mimicking the well-known paradigm of systems medicine (SM) [25]. As an SM, SS takes into account two major aspects: the first is the role of lifestyle in the developmental origins of health and diseases [26, 27]. The second is the ability to understand the deep interactions between the four systems that shape sexual health in general and erectile health in particular: the system of the mind, the system of experience, the system of political and economic choices and, last but definitely not least, the system of the body [28]. Interestingly, these systems must be considered, not necessarily as ED aetiologies, since a direct causative relationship is not always demonstrable in medicine based on evidence, but rather as risk factors for both subclinical and clinical erectile failure.

It is a typical way of reasoning in the light of the SS to admit an inverse *butterfly effect* as that occurring between the political lack of adherence to the green economy, the consequent increase of pollution, the presence of microplastics and endocrine disruptors in the environment, and, finally, reproductive and sexual consequences such as hypogonadism, morphological genital alteration, and ED in a single individual [29]. Similarly, states and political and religious powers supporting negationists and anti-vaccine groups, thus hastening the spread of the virus, could be considered risk factors for the sexual long-COVID, peculiarly represented as ED, occurring during and after complex COVID diseases [30, 31]. Finally, it is a typical lesson from SS to admit that the large majority of ED risk factors are related to behaviours, acted out, or endured, producing various degrees of inflammation at tissue level which may produce endothelial dysfunction as seen in virtually all cases of ED [32]. More insights on the new SS model can be found in the Chap. 7 of this book.

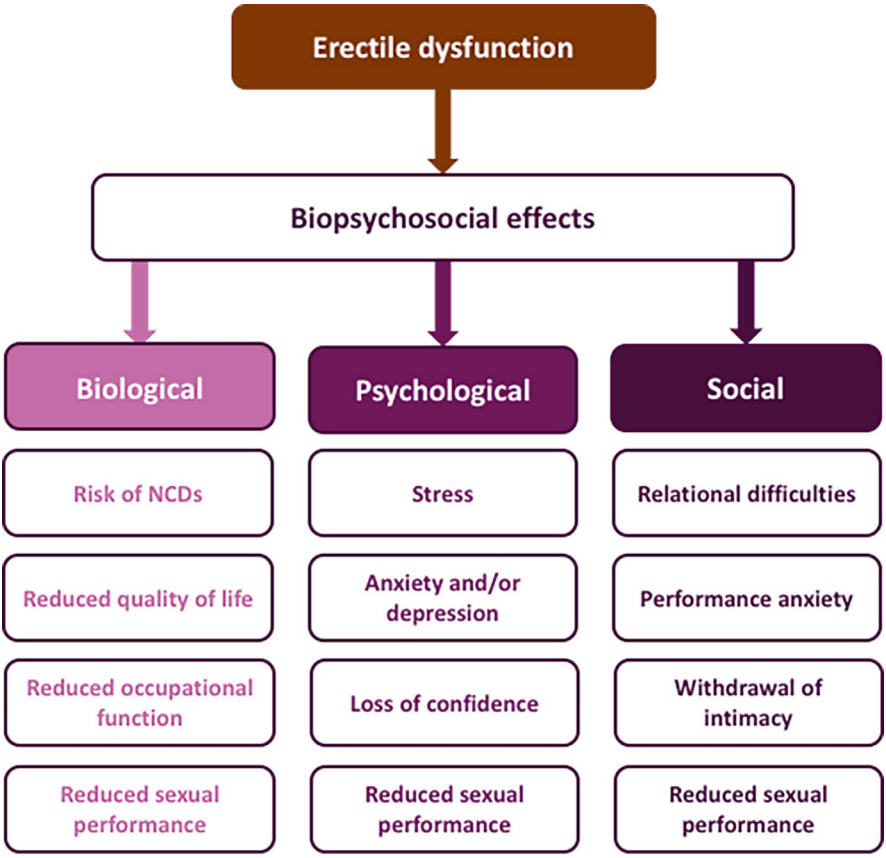


**Fig. 1.1** Impact of ED on patients, considering biological, psychological and social risk factors [21, 23]

Having represented some aspects of the complexity of the ED mechanisms, it is now time to introduce another unusual way to understand this frequent and multifaceted sexual symptom: the *Darwinian perspective*. One of the most striking features of the high prevalence of ED is how contradictory this may be seen within the context of evolutionary biology. Charles Darwin's by natural selection [33] emphasises the survival of the fittest within a species, with fitness denoting the probability that a characteristic will be reproduced. How do we reconcile the high prevalence of ED with the evolutionary imperative of survival of the fittest according to the Darwinian dogma? Moreover, in species that sexually reproduce through copulation, coitus should be particularly protected to increase the chance of reproduction, which is more important for the survival of the **selfish gene** than for the survival of the individual itself [34, 35]. But, apparently, this does not seem to be the case for humans. The next paragraphs of this chapter seek to explore this issue by analysing the evolutionary basis of sexual functioning, drawing an evaluation of ED through an evolutionary lens with an unusual focus on the loss of the penis bone as a key

factor in ED prevalence in humans, thus attempting an evolutionary explanation for ED risk factors, and finally proposing the implications of a neo-Darwinian perspective of ED for its prevention and effective treatment.

## 1.3 Evolutionary Basis of Sexual Functioning

It is accepted that both human and animal anatomy and physiology are influenced by the mechanism of survival of the fittest or, in other words, by the **natural selection** [36]. The underlying principle of natural selection is that the survival and reproduction of individuals and, thus, of species depend on the differences in phenotype [33]. Traits that are linked to anatomical, biological, physiological and behavioural phenotypes may be selected over generations when they facilitate individual advantages and individual survival or those of the species. Typically, the selection of traits is more likely when species are adapted to their environments [36]. However, other important traits may also be selected based on the particular preference of mating partners.

**Sexual traits** (frequently also identified as 'sexual ornaments') are often subject to an ontogenetic force that is at least comparable to that of the mentioned natural selection: **sexual selection**, a form of selection that is representative of the reproductive success of individuals and of the final survival of species [37]. While natural selection is linked to the overall struggle for survival and includes elements of reproduction, sexual selection is focused on mate choices and strategies, successful copulation, the production of offspring, and reproductive advantage, which are key drivers of selection, even where no physical advantage is apparently evident.

One example of sexual selection can be seen in the peacock's tail feathers (train), where extravagant displays of eyespot feathers play a role in attracting a mate. As Darwin—probably the greatest proto-sexologist ever—genially hypothesised in his second book, *The Descent of Man* [37], the evolution of the peacock's train occurred as a result of female preference to mate with males with this phenotype. It was not until more than a century later, in 1991, that evidence supporting this theory emerged in scientific literature, showing that females approach multiple males prior to mating but invariably select the male with the greatest number of eyespots on his train [38]. Further evidence showed that mating success was associated with the presence of these eyespots (when removed, mating success was reduced) [39]. The peacock's tail is a typical sexual ornament used for **intersexual competition**, i.e. typically in the heterosexual setting, to obtain the sexual attention of certain individuals [40].

The question remains as to why a female should choose a male based on this phenotypic trait when it does not necessarily confer any direct advantage from a reproductive standpoint. Indeed, the peacock's train does not contribute towards protection from predation, paternal care or any other physical benefit that may have a practical advantage for survival. Conversely, the larger the train of the peacock, the more likely that the male is vulnerable to predation [41]. As with most sexual traits, the peacock's train size is an evident handicap that should have disappeared according to natural selection if another driver, sexual selection, does not support its maintenance and development in the species. The **Theory of Handicap**, based on

the Handicap Principle, postulates that sexual traits are, in the majority of cases, handicaps that represent a phenotypic condition, which may provide support for sexual selection (Box 1.1).

**Box 1.1: The Handicap Principle**

The handicap principle is the disputed but robust hypothesis proposed by the Israeli biologist Amotz Zahavi in 1975 [42–44]. Key elements of the theory are noted below. Interestingly, the theory was later supported by game theory models and successfully applied to several human contexts [45].

1. Secondary sexual characteristics are **costly** signals.
2. Sexual traits must be **reliable** as they cost the signaller resources that individuals with less of a particular trait could not afford.
3. Individuals of greater biological fitness signal this through handicapping behaviours or morphological traits that **lower overall fitness**.
4. Sexual traits selected through Darwinian sexual selection work as conspicuous consumption, signalling the **ability to afford to squander a resource**.
5. The receivers select signals indicating quality because inferior-quality signallers are unable to produce such **wastefully extravagant signals**.
6. A sexual signal is reliable if the **cost** to the signaller of producing it is proportionately lower for higher-quality signallers than for lower-quality ones.
7. A handicapping sexual trait delivers the hidden message that the carrier or signaller **survived *despite* the handicap**, thus showing great fitness and, finally, better genes.

Phenotypic strength or quality is a key factor that infers genetic quality, which should be favoured in a mate according to the selective pressures of evolution [46]. In this example, it is hypothesised that the peacock's train may be an honest signal of phenotypic quality: peacocks with the highest phenotypic individual quality can survive the physical imposition of a large train, but those with low phenotypic quality cannot [41]. Therefore, the peacock's tail is potentially an important phenotypic signal of genetic quality; only the fittest (or the strongest, smartest or luckiest, according to different perspectives) can afford to maintain an elaborate train for attracting females. In other words, if a certain peacock survived despite the evident handicap of his long and coloured tail, which makes the individual more prone to predation, the individual is likely to carry better genes compared to others with a humbler (and safer) tail.

The potential for traits/ornaments that are prone to sexual selection to signal underlying phenotypes is an important concept when applied to other facets of sexual functioning, including ED. Erectile function may be considered an important phenotypic trait that not only facilitates successful reproduction but may also signal wider attributes of the male. The ability to maintain an erection is crucial to sexual

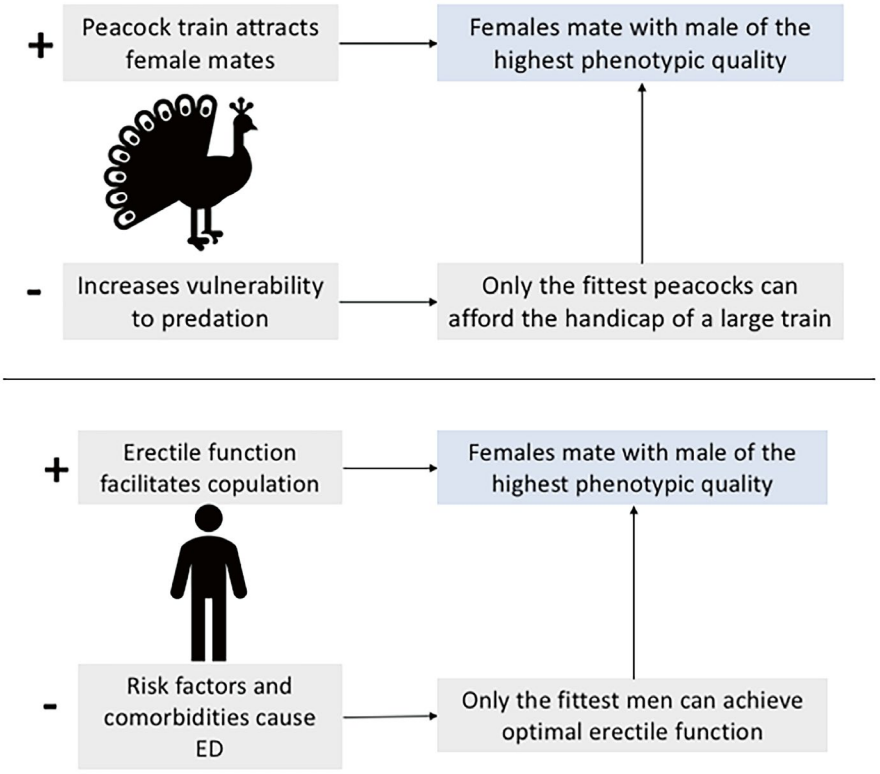


**Fig. 1.2** Conceptual diagram of male-mating strategies from an evolutionary perspective. This figure illustrates how male-mating strategies, such as the peacock train and erectile function in humans, necessitate the fitness of the males due to the potential vulnerability imposed by these mating strategies

reproduction, and this is compromised in patients affected by ED. Importantly, ED is more common in those with a range of health conditions and with a high risk of future conditions that may be indicative of poor phenotypic quality [47]. Therefore, **ED may be defined as a condition-dependent phenotypic trait, whose expression is linked to the health of the individual** [48] (Fig. 1.2).

To further explore this hypothesis, the remainder of this chapter considers how ED may be viewed through an evolutionary lens in relation to the loss of the baculum and the risk factors that underlie the development of ED in humans.

## 1.4 Understanding Erectile Dysfunction Through an Evolutionary Lens: The Baculum

The **baculum,** or **os penis**, is a penile bone found within the distal half of the penis in the vast majority of mammals (Fig. 1.3) [49]. The baculum is formed through the ossification of the distal region of the corpora cavernosa and is located above the

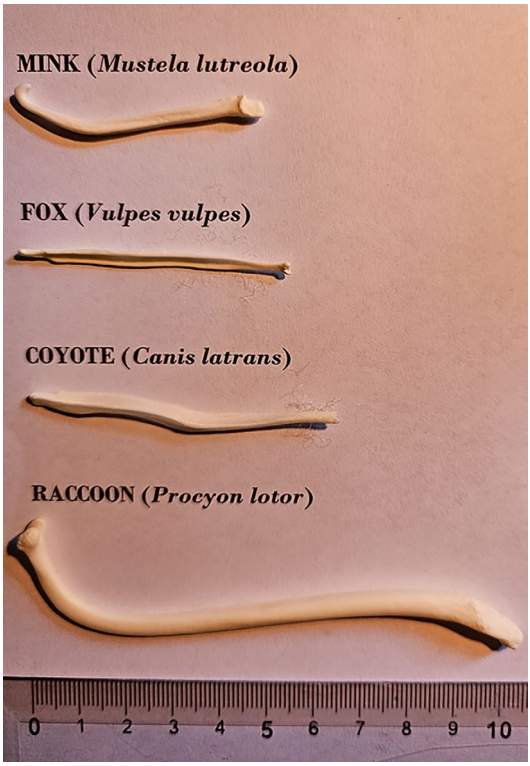


**Fig. 1.3** Baculi from different mammals (EAJ's collection). The ruler is in centimetres. Note the difference in dimension and shape. (Figure reproduced with permission from EAJ)

urethra [50]. The baculum has been described across numerous mammalian orders, including in primates [51]. However, it is notably absent in humans, but chimpanzees, our closest relative, still possess a baculum [52]. In many species, the baculum is hypothesised to play an important role in reproductive success [53].

The baculum, in animals where it is present, i.e. the majority of mammals, is governed by a voluntary skeletal, muscular apparatus known as the **retractor penis** [54]. In Fig. 1.3, the insertional groove can be easily identified in the penis bones. The mechanism through which the baculum operates reflects a key role in providing a simple and affordable supportive structure for erection, rather than relying on the rigidity of the soft tissue of a reproductive organ, governed by a complex and aleatory psychoneuroendocrine and vascular mechanism. When required during sexual activity, muscular contraction facilitates the protrusion of the baculum into the penile sheath [49]. This leads to the stiffening of the erect penis and facilitates copulation. The baculum may be beneficial in a reproductive context, not only in helping the rigidity of the erection during penetrative intercourse but also in maintaining and supporting erection during sexual performance, particularly in species with prolonged intromission [53, 55]. In addition, the baculum has been hypothesised to play a role in reducing sperm competition, with the morphology and length of the baculum correlated with paternity in some species [53, 56]. It has also been suggested that the baculum may serve to orient the female towards a specific male partner and, at the same time, cause damage to the female reproductive tract to

prevent subsequent mating with another potential partner [53, 57]. It may also stimulate female ovulation or implantation in some species, with baculum length tending to increase in species with induced ovulation [57]. The baculum may also be seen as a signal of male quality, with morphology and length providing a phenotypic marker of fitness [53], perhaps—we can hypothesise—useful for intrasex and/or intersex competition.

While there are several hypotheses over the exact benefits of the baculum and the mechanisms through which it facilitates reproductive success, it is evident that species with a baculum have this structure as an aid to reproduction and do not rely solely on the engorgement of the penis with blood to allow erectile function. However, the evolutionary profile of the baculum's morphology and function suggests that the penile bone may have undergone variations and adaptations corresponding to environmental and sexual selection pressures. These pressures may have impacted its morphology as well as its presence.

The evolutionary history of the baculum in primates suggests that this structure has been gained and lost over many lineages [53, 58, 59]. It has been suggested that the baculum has been gained at least nine times and lost at least ten times throughout mammalian evolution [53]. As with genital morphology, it has been suggested that the shape of the baculum is dependent on sexual selection [49]. Notably, the evolutionary history of the baculum also reveals considerable variation in the morphological characteristics of this bone [58]. Experimental data have also supported the role of sexual selection in the determination of baculum morphology. For instance, the modification of the sexual selection processes in populations of house mice led to changes in baculum morphology. Specifically, when post-copulatory sexual selection pressure was artificially increased, after 27 generations, mice showed significant thickening of the baculum compared to those in populations where enforced monogamy was established (thereby reducing sexual selection pressure) [58].

These findings support the idea that sexual selection and associated pressures may influence the evolution of the baculum. The assumption follows that populations where sexual selection pressure is high, including those with seasonal mating and in polygamous systems, will be subject to stronger evolutionary forces [49]. Conversely, where sexual selection pressures are low and monogamy prevails, evolutionary forces may be less relevant in influencing baculum morphology and preservation. This explanation is not entirely applicable to humans, a species we might define as **monogamous-unfaithful**. Indeed, monogamy gives humans the enormous adaptive advantage of being able to support fragile and immature children. These advantages may have the same specific adaptive weight as those produced by renewed genetic opportunities obtained from extra-pair mating. As a result, since the vector of monogamy is equally and oppositely powerful to that of infidelity, humans are the only animals fully endowed with free will in their sexual choices, despite being largely influenced in these by the four systems explored by the SS, the systems of the mind, experience, society, and, of course, the body. Moreover, in humans, the substantial **loss of oestrus** and the **concealment of ovulation**—two critical and specific sexual functions—have shaped human sexual behaviour as it appears nowadays [60].

Between primates, humans are almost unique in having lost the baculum during differentiation from common ancestors. The exception seems to be the *Ateles*, a genus of New World monkeys (platyrrhines) that also lack a baculum [61]. The absence of the baculum in *Ateles* represents a separate evolutionary path from humans, who are Old World primates (catarrhines). This implies that baculum loss occurred in a few primate lineages, not only in the human lineage, allowing us to suggest that platyrrhines are perfect animal models to study ED and male peripheral reactions instead of rodents, which are unfortunately largely used in the scientific literature for both erection and ejaculation studies.

A few theories have been proposed to explain the loss of the baculum in humans as a result of sexual selection. Some of these posit that the loss of the baculum is a means for females to evaluate male health [35] and that it may have occurred in response to decreased post-copulatory competition and increased monogamy, which require shorter intromission [62]. Additionally, the tactile stimulation hypothesis proposes that the female choice for tactile stimulation and the possibility of enjoying a larger range of copulatory positions facilitated a boneless penis [63]. Other theories hypothesised the advantage in preventing the risk of penile blunt trauma associated with upright posture and a possible role in intrasex competition [52]. These theories are summarised in Fig. 1.4.

Collectively, these theories provide a basis for explaining how changes in mating systems may have reduced the need for the baculum while also highlighting how sexual selection processes may be influenced by baculum loss.

The presence of baculum in ancestral primates suggested that the *os penis* first arose at the time of the split of non-placental/placental mammals and the most recent common ancestor of primates and carnivores [49]. Examining the symplesiomorphy—i.e. how an ancestral characteristic is shared by all members of a clade, including both genders of a species—early analyses showed that the female

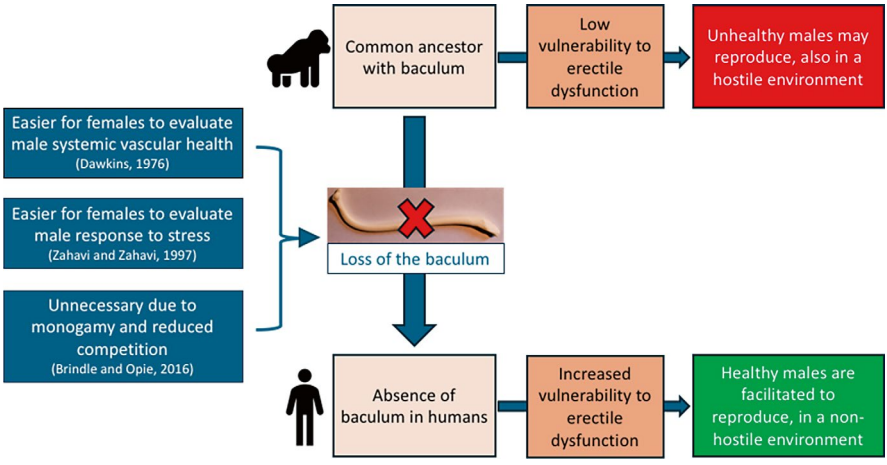


**Fig. 1.4** Overview of theories for baculum loss in humans, with supporting evidence/studies and with the modified Dawkins's adaptive theory. (Adapted from Smith and Hechtel [62])

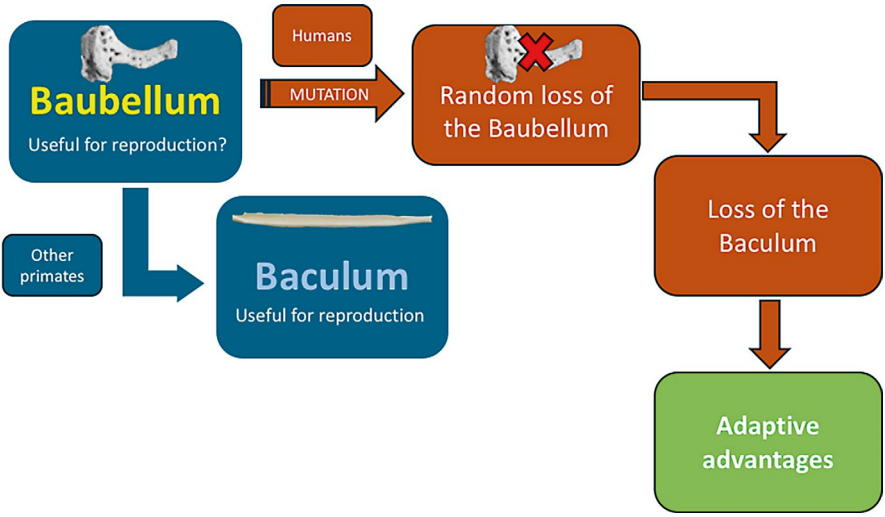


**Fig. 1.5** The Jannini theory of baubellum-baculum. For the ontogenesis of virtually all male dimorphic genital tissues, an undifferentiated/female template is needed. Just as the clitoris is the anatomical and functional model on which the penis is formed during prenatal ontogenesis, so the baubellum is be considered the template of the baculum. Nevertheless, being apparently non-essential to reproduction, the baubellum has been lost in some primates. The random disappearance of the baubellum's template caused the loss of the baculum, which generated unexpected advantages in some species, like humans

counterpart of the baculum, the **os clitoris** or **baubellum**, has been lost more frequently during evolution. In particular, among 163 studied species, apparently 29 have a baculum but not a well-developed baubellum [64]. However, a more recent phylogenetic analysis, confirming the baculum/baubellum homology, found that for each baubellum, a baculum was invariably present [61].

The latter evidence may not help solve the conundrum. The baubellum may be hypo- or non-functional with respect to reproduction itself and thus randomly lost over time, but why is the baculum also lost despite its important role in protecting the erection needed for the survival of species? As with other genital tissues, the baculum is the modification of the baubellum occurring during ontogenesis in the presence of masculinity-driving genes and hormones. The absence of a clear-cut utility in non-matriarchal species (where clitoral exhibition may help gain an alpha rank) may have led to the disappearance of the baubellum, which in turn drove the loss of the baculum. Interestingly, this generated gender-specific consequences (Fig. 1.5).

We may hypothesise here that the loss of the baubellum in women may have increased the chances of having a **female orgasm**, a function poorly studied and perhaps rarely and questionably observed in animals. Although in some species the baubellum seems related to the stimulus of ovulation [65], the coitus for several female animals is frequently painful instead of pleasurable. The absence of the bone in the human clitoris, coupled with the replacement of a potentially painful baculum

by softer tissues, may have facilitated the emergence of the human clitoral orgasm [66].

However, a major adaptive advantage of the disappearance of the baculum could be hypothesised in the males of our species. We may theorise that this mutation played and plays an important feature not only in how females evaluate the fitness of males from an evolutionary perspective, as suggested by Dawkins [35], but also in producing an efficient and powerful **adaptive mechanism** that makes copulation possible only for psychologically, relationally and physically healthy individuals acting in a non-stressing environment. In fact, after losing the baculum during evolution, human male erectile function was no longer a voluntary action [2]. The pivotal machinery for developing and sustaining an erection in humans relies on factors such as the presence of an efficient tunica albuginea, the activity of a healthy endothelium, and the relaxation of **smooth muscle cells** within the cavernous tissue, allowing for an increased input and a decreased output of blood to and from the corpora cavernosa, leading to increased blood pressure in the penis [67]. While Dawkins put forth the handicap theory of baculum loss, which allows females to evaluate males' fitness, specifically for vascular health, it is important to add here that, in humans, reproduction is not only based on female choices and that erectile function does not only represent a vasculogenic process nor just a physical one. Erectile function in humans is influenced by a complex interplay of factors, including environmental, psychological, relational, endocrinological, neurological and vascular [2]. The voluntary control of erectile function, if any is maintained at all, may have a greater negative influence on function rather than a positive one [48]. Therefore, understanding ED as a signal of health and male response to stress—both related to health and environmental factors—may be a more rigorous hypothesis, reflecting the diverse factors that influence erectile function.

The core of our hypothesis is that the loss of the "useless" baubellum and, consequently, of the baculum, has generated a mating strategy according to which the healthiest individuals (not necessarily and exclusively those selected by the partners) are facilitated in reproduction, consistent with the principle of the reproduction of the fittest (healthiest), and finally solving the *Darwinian paradox* of the loss of a very strong support to the reproductive power, such as is the penile bone. The absence of the baculum produces a detrimental effect on an individual (as an unfitting person may fail to reproduce), but it may also possibly confer an overall great advantage by accelerating the evolution of the human species. This is exactly what happens in animal societies dominated by alpha females and/or males (wolves, lions, deer, etc.), where (almost) only the alpha individual reproduces while all other animals with lower individual characteristics are condemned to being unable to pass on their genes to future generations [68, 69]. In the case of these **intrasexual** (i.e. agaist the individuals of the same sex) **competitions**, the selection for reproduction of more fitting individual characteristics compared to others weaker is probably lower with respect to that expressed by the modulation obtained with a more comprehensive selection generated by the 'absolute' environmental, intrapsychic, relational and biological health (Fig. 1.6).

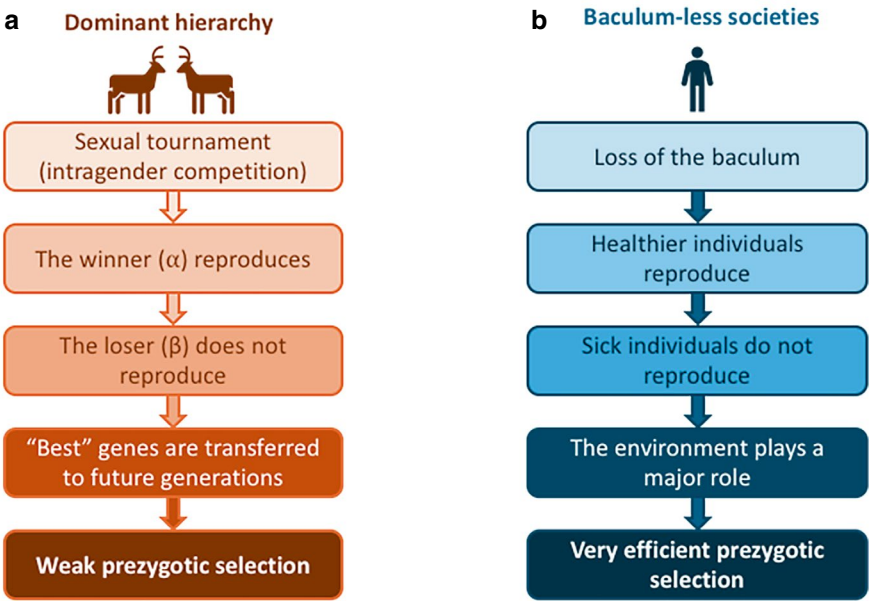


**Fig. 1.6** Comparison between two prezygotic selection strategies. Ethologically, an animal society is based on a *dominant hierarchy* (**a**), where members interact to create a ranking system, in which a dominant higher-ranking individual is called the 'alpha' and submissive, lower-ranking individuals are referred to as 'beta'. One of the advantages of these hierarchies is that rather than fighting each time they meet, individuals of the same sex establish a relative rank, with alpha individuals often having the right to mate. This strategy should select for good genes, but in reality, it is potentially effective only in relation to another individual (in this case, the loser in the sexual tournament). The disadvantage is that a very large number of individuals do not reproduce. Conversely, in *baculum-less societies* (**b**), reproduction is possible and easy in several healthy individuals within a healthy environment. While the first strategy is 'relatively' efficient, the second one is 'absolutely' more efficient for selecting more fitting individuals and healthier pups

This hypothesis can be further supported by evaluating the role of evolution in relation to **risk factors** for ED, illustrating the importance of baculum loss as a mechanism through which erectile function serves as a signal for phenotypic quality.

## 1.5 Evolutionary Explanations for ED Risk Factors

The development of ED and the risk factors associated with this condition have been extensively studied across populations [23, 70, 71]. Risk factors for ED may be categorised to align with the complex aetiological drivers of the condition, including systemic biological factors and relational and intrapsychic factors [2]. A summary of the key risk factors for ED is presented in Table 1.2.

From a biological perspective, risk factors for ED tend to reflect advancing age, the influence of lifestyle factors or the presence of a hostile environment, producing distress in individuals [2]. Advancing **age** is one of the clearest risk factors for ED,

**Table 1.2** Summary of key risk factors for ED

| Category/type of risk factor | Risk factors |
|---|---|
| Lifestyle | Smoking<br>Obesity<br>Physical inactivity<br>Excessive alcohol and drug consumption |
| Systemic | Organ and system insufficiency and failure (lung, kidney, etc.)<br>Cancer<br>Other systemic diseases (e.g. genetic and autoimmune diseases, infections, etc.) |
| Cardiovascular | Hypertension<br>Cardiovascular disease |
| Metabolic | Type 2 diabetes mellitus, gout, etc. |
| Hormonal/endocrine | Hypogonadism<br>Hyperprolactinemia and other pituitary disorders<br>Hyperthyroidism and hypothyroidism<br>Cortisol disorders |
| Neurological | Spinal cord injury<br>Epilepsy<br>Specific neurological conditions (multiple sclerosis, Parkinson's disease) |
| Urological | Lower urinary tract symptoms (LUTS) and chronic prostatitis<br>*Induratio penis plastica*<br>Penile structural abnormalities |
| Iatrogenic | Drugs interfering with testosterone activity and metabolism<br>Anti-psychotics or antidepressants<br>Pelvic surgery |
| Psychiatric, psychological and relational | Affective disorders (depression, anxiety, etc.)<br>Psychoses<br>Negative education and experiences<br>Low self-esteem or confidence<br>Relational difficulties (poor communication, impaired couple fitness) |
| Sexual | Hypoactive sexual desire disorder<br>Ejaculatory disorders (LCEE, loss of control of erection and ejaculation)<br>Partner sexual disorders<br>Infertility (infertosex syndrome)<br>Couplepause/doublepause |

Note that the anti-erectile mechanism of action of these risk factors is, in the large majority of cases, acute or subacute *inflammation* and that the specific lesion of the *endothelium*, in general, and that of the corpora cavernosa, in particular, is a consequence of inflammation [2, 72]

with an increase in the prevalence of ED seen in older men [23]. It could be noted here that having an older father in a wild environment may reduce the chances of offspring survival. Indeed, it is to be noted that the majority of ED risk factors accumulate with time or are more likely to affect older men. In fact, particularly in older populations, the development of chronic disease or comorbidities can lead to an increased risk of ill health, suggesting that there are advantages to reducing reproduction in these older age groups to ensure the genetic fitness of future generations. However, as noted previously, age alone may not be the full story in explaining the

increased likelihood of ED with advancing years. Indeed, **lifestyle**-related risk factors accumulate over time and become more likely in age groups where ED is common [2]. These lifestyle factors are diverse and include smoking, obesity, physical inactivity and the consequences of disease processes, such as hypertension, metabolic syndrome, diabetes mellitus and psychiatric neurological, endocrine, cardiovascular, toxicological and systemic conditions (e.g. respiratory and oncological diseases)—all meeting the definition of **chronic non-communicable diseases** (NCDs) [2]. Interestingly, parasites, viruses and bacteria may also be linked, directly or indirectly, to ED. A common factor seen in communicable diseases and NCDs is **inflammation**, the mechanism of action of endothelial failure, which is considered the most frequent reason for erectile weakness or impairment [73]. In other words, the loss of the baculum has favoured the survival of species with the best fitness, where only healthy individuals can successfully and reliably achieve an erection and thus, by means of copulation, reproduce.

**Intrapsychic** and **relational** risk factors have also been identified in relation to ED [2]. Intrapsychic factors underscore the proposed importance of the link between biological and psychological functions during sexual performance. Specifically, negative attitudes or experiences related to sexual performance may interfere with cues for sexual arousal, linking psychological/cognitive processes impacting biological mechanisms [23]. Low self-esteem, sexophobic education, negative experiences, egodystonic sexual orientation, gender issues in homo−/bi−/transphobic environments, depression, anxiety and psychoses may all potentially contribute towards negative perceptions of sexual performance, failure prevision, avoidance of sexual activity and loss of sexual intimacy, finally resulting in ED [72, 74]. In other words, only individuals psychologically and psychiatrically healthy may copulate and reproduce, thanks to the loss of the baculum. Interestingly, relational dynamics may also contribute to the negative cycle of psychological influence on erectile function, with partner expectations, judgment, lack of communication or relationship satisfaction potentially contributing to ED [75]. When there are existing physiological risk factors for ED, this may heighten the potential for intra-psychic and relational risk factors to influence future sexual performance [23]. In other words, only individuals in a fitting relationship (i.e. in a congruous erotic setting) may be facilitated to copulate and reproduce, again thanks to the loss of the baculum.

This hypothesis is made—apparently—fragile by the possible (although unlikely) presence of an erection in, for example: (i) gender violence (i.e. in the absence of relational health), (ii) in depressed/anxious/psychotic people (i.e. in the absence of intrapsychic health), (iii) in highly stressful conditions, such as famine, epidemy, or war (i.e. in the absence of environmental health), (iv) in initial stages of performing wrong and unhealthy lifestyles (i.e. in absence of correct behaviours), (v) in the initial stages of communicable or NCDs (i.e. in the absence of full biological health). However, it should be considered a biological and reproductive advantage should never work in 100% of the cases. It has been, in fact, demonstrated that mate preference tends to a steady state, or equilibrium, when the benefits of mate choice are sufficiently large relative to the cost of choice [76]. Furthermore, we have to note that in all of the above-mentioned extreme situations, achieving an erection is

much more difficult than under normal, healthy conditions and that the hypothesised mechanisms, to properly work, should just (strongly) favour more fitting individuals and settings.

One could also argue, against this explanation, that ED appears to be associated with diseases characteristic of modern society [52]. But this argument seems fragile, given that virtually all diseases, even those that characterize archaic human life, such as infections and trauma, can be important risk factors for ED. Vice versa, the **handicap** (working as an advantage) **of the loss of the baculum** increased its selective power with the rise of more complex diseases, related to modern lifestyles, such as NCDs, *bona fide* much less present in primitive societies.

Another comparison with the female counterpart may help thrust the hidden benefits of baculum loss, further supporting our hypothesis. This can be achieved by comparing the mechanisms that regulate oogenesis in human females and those that produce ED in males [77]. For instance, females are born with a finite number of oocytes, which are typically released during monthly ovulatory cycles, from puberty to menopause. Consequently, once oocytes are depleted, the age at which a female can reproduce is naturally determined, avoiding risks of pregnancy and childbirth in older age groups. The prevalence of ED in men without a baculum is dramatically age-dependent; this characteristic reduces the menace of high-risk pregnancies with increased prevalence of dangerous mutations and also reduces the possibility of a too late parenthood for effective care of the typically immature offsprings of the human species. In other words, since men do not experience the same mechanisms as menopause, which exerts a highly effective **pre-gametic** blockade, the decline in testosterone and the difficulty in achieving and maintaining an erection, typical of the so-called andropause, counteract the aforementioned (over)production of spermatozoa throughout a man's life through a mechanism we might define as **pre-copulatory**. But there is more. When focusing on the monthly ovulatory cycle, it is notable that successful ovulation depends on the environment and health, with environmental stressors and ill health potentially causing ovulation to cease. This may be further viewed as an efficacious protective mechanism (again, far from acting 100% of the time) against reproduction during periods of distress in the environment or during poor individual/couple/species health conditions. Having to target only one egg cell per month, this gear is particularly effective in reducing, if not inhibiting, ovulation, fertilization, implantation, pregnancy and even puerperium in the presence of hostile or risky environments and psychological, relational and physical problems. However, it cannot have the same efficiency in males, who are capable of continuously producing a huge amount of sperm from puberty through to old age [78]. In other words, as above mentioned, blocking one single egg per month (or interrupting a fragile pregnancy or puerperium) is much easier than blocking millions of spermatozoa produced by the testes. Therefore, both pre- and post-zygotic interference-from the environment and from psycho-relational and physical events-on females, aims at facilitating reproduction under optimal conditions, a strategy which cannot be applied to males with the same efficiency. A completely pre-zygotic and pre-coital selection mechanism is required, as provided by the loss of the baculum (Fig. 1.7).

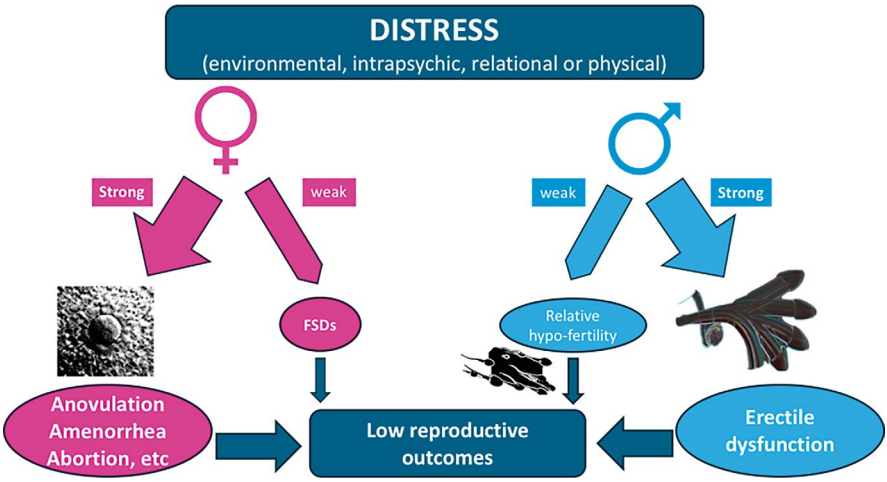


**Fig. 1.7** Gender differences in the effect of distress on reproduction. The same di-stressor produces two strong effects in females (from anovulation to abortion) and males (erectile dysfunction), with two mechanisms quite efficient in blocking reproduction, as the arrow sizes indicate. Conversely, the reproductive output itself is *relatively* less dramatically and less universally affected by distress-induced female sexual dysfunction (FSD) and by the effect on spermatogenesis

One may argue that psychological and physical diseases, environmental toxins and distress also affect spermatogenesis. This is true as the same mechanisms act very negatively on females by producing several female sexual dysfunctions (FSDs). However, both pathological processes are characterised by low efficiency in blocking the reproductive output. Distress-induced, communicable-disease-induced and NCD-induced complete azoospermia is rare, or non-existent (in contrast to oligospermia) [79], and distress-induced, communicable disease-induced and NCD-induced FSDs certainly produce a barrier to reproduction [80], but no one is per se able to efficiently fully block it [81]. Anovulation/abortion and non-baculum-dependent ED, as on-off systems, appear much more efficient.

## 1.6 Other Advantages of the Loss of the Baculum

When considering the ancestral versus the modern environment, it is important to note how priorities in sexual performance and the need for the baculum may differ in modern men compared with ancestors and other species. For instance, the need for a quick erectile and ejaculatory process is recognised as important in ancestral hominids and in other species, and the baculum may facilitate a quick ejaculation (*coitus citus*. Lat: coitus as fast as possible) [82]. This reflects the advantage of speed in depositing semen to impregnate the mate, thus achieving the potential for reproduction [83]. This may be particularly advantageous where pressures exist in the environment, such as sexual selection pressures (other mates) or the risk of predation, which favours a reduction in the time spent copulating [83].

In contrast, bonds and relationships from the prehistory of *homo sapiens* reflect different values and approaches to mating than the behaviours seen in polygamous species with high sexual selection pressure [84]. This echoes changes over time and within the species, such as long-term mating strategies, female choice and empowerment in partner selection, value placed on monogamy, and low sexual selection pressure from other mates in the post-copulatory period [84]. Furthermore, the need for rapid ejaculation following the initiation of sexual intercourse is no longer considered essential or favourable. This reflects the aim of human sexuality as one oriented toward pursuing pleasure and heightening the enjoyment of the partner, requiring men to control their ejaculation [83]. Hence, cultural forces have reduced the importance of speed during reproduction, which may also reflect evolutionary adaptations to human relationships and society over time.

## 1.7 Implications for Treatment and Prevention: Inhibiting Type 5 Phosphodiesterase as the New Baculum

A range of factors contribute to the development of ED in humans, including biological, environmental, relational and intra-psychic. This constellation of factors may be seen, to varying degrees, in all patients presenting with ED, highlighting the multifactorial nature of this clinical condition. An understanding of these factors and how they relate to lifestyle choices provides an opportunity for the prevention of ED as well as the targeted management of the condition when it presents.

The **prevention** of ED at the population level is vital from a public health perspective. The consequences of ED on individuals and partners/relationships can be profound and can impact not only sexual performance but also wider well-being. However, it is particularly important to consider the prevention of ED as being justified, considering that ED can be an early signal of poor health. Preventative strategies targeting lifestyle risk factors have the potential to not only reduce the likelihood of ED but may also confer wider benefits for human health, including reduction in cardiovascular risk, as explored in Chaps. 2 and 5. The importance of ED prevention and treatment in the context of 'diabesity' (Chap. 3), psychological conditions (Chap. 4) and endocrine disorders (Chap. 6) will also be considered.

Once ED presents, effective treatment is crucial to minimise the impact of the sexual symptom. Historically, treatment options for ED were limited to and relied mainly on aphrodisiacs or alchemical practices, with **psychotherapy** later introduced as a therapeutic approach in the early twentieth century [4]. In the 1970s, an alternative to psychotherapy was the use of exogenous **androgen therapy** [85]. In the 1980s, malleable penile implants and inflatable **prostheses** were introduced [86]. While these devices and prostheses remain in use today, non-invasive strategies remain more desirable for the majority of men affected by ED. It was only in 1998 that the first approved pharmacological approach to managing ED was introduced to practice in the form of oral tablets of **sildenafil** citrate, a powerful and well-tolerated phosphodiesterase type 5 (PDE5) inhibitor [87, 88]. Consequent to their introduction in practice, PDE5 inhibitors (PDE5i) have become the most common intervention for ED and are recommended as first-line therapy, regardless of

the underlying cause, when the removal of the contributing risk factor is impossible or insufficient to restore erectile function [2, 89]. An overview of contemporary treatment options for ED is presented in Table 1.3.

The development of PDE5i for use in managing ED is one of the most widely known instances of serendipitous discovery in modern times. This class of drugs was initially developed to treat angina by promoting smooth muscle relaxation, but patients were observed to develop nocturnal and spontaneous erections during evaluation [90]. These effects led to a change in focus towards the use of PDE5i in sexual medicine and the management of ED. The mechanism of action of PDE5i involves the amplification of the **nitric oxide** (NO) - **cyclic guanosine monophosphate** (cGMP) pathway [91, 92]. This pathway includes the production of NO in nerve endings and vascular endothelial cells in response to physiological sexual stimulation. NO is, in turn, responsible for increasing cGMP, a regulatory of calcium channels, leading to the closure of these channels and a decrease in intracellular calcium. This results in smooth muscle **relaxation** and the vasodilation of the

**Table 1.3** Overview of the treatment options for ED [2]

| Therapeutic intervention | Details |
|---|---|
| *Aetiological approaches* | |
| Lifestyle modification | Healthy diet/Mediterranean diet to prevent or manage obesity, metabolic syndrome, and diabetes mellitus<br>Physical activity to reduce weight or prevent obesity and diabesity<br>Smoking and other drug cessation<br>Moderation in drinking alcohol |
| Aetiological therapies | Addressing or reducing the sexual impact of the underlying risk factor (e.g. curing cancer or renal failure, etc.) |
| Hormonal therapies for endocrine conditions | Testosterone replacement therapy in hypogonadism<br>Targeted management of pituitary, thyroid and adrenal dysfunctions |
| Psychological therapies | Counselling<br>Psychoanalysis to be considered where other approaches have failed |
| *Symptomatic approaches* | |
| Oral pharmacological agents | Oral PDE5i as a first-line option for managing ED in all eligible patients, both in the traditional film-coated pills or in the newer orodispersible films that specifically respect patient intimacy |
| Psychotherapies | Sex therapy (e.g. cognitive-behavioural therapy to be integrated with other psychotherapeutic interventions and lifestyle changes) |
| Intra-urethral or intra-cavernosal administration of vasoactive substances | Alprostadil in men where PDE5 inhibitors are contraindicated, not tolerated or ineffective |
| Physical therapies | Vacuum devices may be considered where pharmacological options are contraindicated or not effective<br>Low-intensity shockwaves |
| Surgical therapies | Penile prostheses must be considered where other options are contraindicated or not effective |

Note the distinction between aetiological (when the underlying risk factor is specifically addressed and possibly cured) and symptomatic (when the therapy aims to reduce the impact of the symptom on the sexual and relational quality of life of the couple) approaches

arteries in the penis, leading to the engorgement of the corpus cavernosa with blood, i.e. the **erection**. The PDE5i specifically act by competitively inhibiting the "erectolytic" PDE5 enzyme, which is responsible for the breakdown of cGMP into GMP. Sildenafil thus promotes erection and penile hardness stabilizing the effects of cGMP, such as smooth muscle relaxation and enhanced penile blood flow [90].

## 1.8 Conclusion: The Loss of the Baculum and the Canary in the Coal Mine

The genial neo-Darwinian scientist John Burdon Sanderson Haldane (1892–1964) first intuited that thalassemia (and, later, sickle cell anaemia), a severe genetic blood disease, was much more prevalent where malaria was also present, prompting the hypothesis that mutations in carrier families likely persisted because they offered some protection against malaria in these malaria-endemic geographies [93]. In this case, a severe individual handicap (i.e. the genetic disease leading to various acute and chronic complications, several of which have a high mortality rate) remains in the population because it confers an immediate advantage in the survival to a mosquito-borne, lethal infectious disease such as malaria.

Similarly, the persistent and sexually selected disappearance of the baculum, despite the evident handicap affecting the ability to copulate and thus to reproduce, produced the advantage of selecting more healthy *carriers of genes* in a healthier environment coupled with a more fitting partner, which may have powerfully boosted human evolution. This perfectly fits the criteria of the handicap theory mentioned above.

We suggest here that ED is a signal of poor phenotypic quality and, as such, reflects the pressures of evolutionary sexual selection in humans. The development of ED may be a sensitive and early marker of wider disease processes and vulnerabilities that are less desirable in mates and subsequent offspring. *The loss of the baculum gave rise to ED*, a symptom that is probably rare, if not virtually unknown, in the animal kingdom and transformed ED itself into the **best biomarker** able to early predict, as this book largely demonstrates, virtually all external and internal factors discouraging reproduction. We can easily infer here that the loss of the baculum played a major and unique role in accelerating the entire process of human evolution by facilitating and selecting, through a strong and efficient *pre-zygotic mechanism*, the reproduction of individuals displaying vascular, endocrine, neurological, immunological, oncological, systemic, toxicological, psychiatric, environmental, intrapsychic and relational health. No one human symptom could be considered as powerful as ED as an early biomarker of general and environmental health—hence the perfect *canary in the coalmine*.

The growing role of lifestyle factors in the population's overall health and wellbeing, including their key contribution to the development of communicable- and NCDs, may be linked to the rising prevalence of ED. It could be, therefore, imagined that a "prehistoric" or at least "pre-industrial" life might have been advantageous from a sexual and reproductive perspective. However, this is not the case, because there is another aspect to consider. Thanks to advances in modern

medicine, humans fortunate enough to live in affluent regions of the planet now enjoy better overall health than ever before. At the same time, they enjoy an incredible ability to address sexual symptoms (in the case of men, primarily thanks to the *Viagra Revolution*), despite the growing burden of chronic diseases in society, particularly impacting older age groups. Thus, recent advances in healthcare have enabled better management of the negative effects of modern lifestyle risk factors, just as they have led to an increase in the average human lifespan and associated expectations of health and well-being in old age, including sexual function.

The burden of ED largely affects older populations as a result and imposes fragility on the male sexual physiology in this age group. There is a need to consider expectations of sexual function and pleasure in patients affected by ED, independent of age, to support the delivery of individualised and holistic care according to the lesson of the new SS model (Chap. 7). The treatment of ED is therefore crucial, and there is a need for PDE5i to overcome the "advantageous" fragility of male sexual physiology, which is, after the loss of the baculum, a major sexually selected impediment to reproduction. These drugs are invaluable in improving erectile function and overcoming this evolutionary obstacle [48].

But all these achievements would not be possible without the loss of a little penile bone thousands of years ago and the serendipitous discovery of revolutionary pharmacological support just 30 years ago.

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# Erectile Dysfunction: A Harbinger of Cardiovascular Disease Risk

2

Andrea Salonia and Gerald Brock

**Abstract**

Cardiovascular diseases (CVDs) are a significant source of morbidity and mortality despite improvements in treatment. The recognition of CV risk and the early identification of CVD are crucial to facilitate early intervention and preventative strategies. This chapter presents a critical review of the literature on the role of erectile dysfunction (ED) as an early marker for CVD risk. ED and CVD share a number of risk factors, while ED itself may be considered an important risk factor for CVD, particularly in younger men with arteriogenic ED. Epidemiological data support an association between ED and CVD, with reports suggesting that ED often occurs years prior to the onset of CVD. This reflects the shared pathophysiological mechanisms of ED and CVD and the earlier emergence of symptoms in small-diameter arteries, such as those in penile tissue, secondary to atherosclerosis and endothelial dysfunction. The importance of these observations is considered with respect to the clinical implications of studies exploring the predictive value of ED for future CVD risk. The chapter concludes with clinical insights into the role of ED in CVD risk assessment and the integration of ED assessment in routine CVD health screenings.

**Keywords**

Cardiovascular · Risk · Erectile dysfunction · Pathophysiology · Screening

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## 2.1 Introduction: Connections Between Erectile Dysfunction and Cardiovascular Health

Cardiovascular (CV) health is recognised as an important determinant of a number of health outcomes at the population level [1]. Apart from the morbidity caused by CV diseases (CVD) and the loss of enjoyment of physical activities, it is estimated that CVD mortality accounts for one-third of all deaths globally, equivalent to more than 17.9 million deaths per year [2]. Furthermore, poor CV health is consistently predictive of the risk of cancer, poor quality of life (QoL) and higher healthcare costs [1]. The past few decades have seen dramatic advances in therapeutic interventions for CVD, which have led to improvements in survival in patients with established CVD over time, although these improvements appear to have largely plateaued [3]. Despite improvements in survival, CVD remains an important source of mortality and morbidity once established [4]. Subsequently, there has been an important focus on the need for the early identification of those at risk of CVD in order to facilitate early interventions as well as preventative strategies that can support positive CV health for the index patient and their family members who are at heightened risk [5].

The previous chapter highlighted the importance of erectile dysfunction (ED) as a source of morbidity among men while also emphasising the importance of ED as a marker of fitness from an evolutionary perspective. The presence of ED in men is linked to the loss of the baculum (penile bone present in some mammals) and the increased susceptibility of erectile mechanisms to stressors and disease [6]. Specifically, ED may serve as a marker for poor CV fitness/health during sexual selection, which illustrates the interrelated nature of ED and CVD in men [7]. On this basis, the presence of ED may be indicative of poor CV health and the risk of future CVD in men.

Evidence supporting a link between ED and CVD relates to epidemiological data and pathophysiological observations. Despite growing data depicting an increasing trend in young men presenting with ED in the real-life setting [8, 9], both ED and CVD are more likely to occur with increasing age and are often comorbid conditions, with an increased risk of ED in men with CVD and a higher prevalence of CVD in men with ED than without. The first real-life study in this setting found that ED is present in 49% of men with existing CVD [10], while it has been shown that CVD is 45% more likely to occur in men with versus without ED [11].

Epidemiological studies have highlighted that both ED and CVD have numerous shared risk factors [12]. Risk factors for CVD are well established and include a range of modifiable lifestyle and environmental, as well as non-modifiable, risk factors [13]. Risk factors specific to ED have been identified and overlap with many of these, such as smoking, obesity, diabetes, arterial hypertension and dyslipidaemia (Table 2.1). Meta-analyses support an association between ED and both hypertension (odds ratio (OR) 1.54–1.74) and diabetes (OR 2.08–3.62)—two common CV risk factors [14]. Similarly, dyslipidaemia has been associated with the risk of ED [15], and current smoking behaviour is associated with a 51% increased risk of ED [16]. A similar risk has been observed even for e-cigarette smoking and ED [17, 18].

**Table 2.1** Risk factors for erectile dysfunction and cardiovascular disease

| Shared risk factors for erectile dysfunction and cardiovascular disease |
|---|
| Hypertension |
| Diabetes |
| Dyslipidaemia |
| Cigarette smoking |
| Obesity |
| Low levels of physical activity (sedentary lifestyle) |
| Metabolic syndrome |

Adapted from reference [23]

In a meta-analysis of eight observational studies (including 12,067 men), there was a 2.6-fold increase of ED in patients with metabolic syndrome (MetS), with all components of MetS, other than high-density lipoprotein levels, correlated with an increased risk of ED [19]. It was also shown that men with type 1 or 2 diabetes mellitus have a 3.62-fold increased risk of ED as compared with healthy controls in a meta-analysis of 145 studies (including 88,577 men) [20]. These shared risk factors for ED and CVD are also linked to shared pathophysiological events in these conditions, most notably the contribution of risk factors for vascular endothelial dysfunction as a driver of disease [21]. Indeed, reductions in endothelium-dependent smooth muscle relaxation, endothelial nitric oxide synthase (eNOS) activity and NO availability, as well as oxidative stress and vascular hypertrophy, have all been associated with common CV risk factors [22].

The potential for ED to be linked to CV health is an important observation in published literature, reflecting the evolutionary role of ED as a marker for CV fitness. Importantly, the presence of ED may be considered not only a complication of CV risk factors but also an early sign of future CVD [12]. This is a key consideration as the emergence of ED prior to the onset of other CD manifestations may have value in clinical practice. Montorsi et al. [10] have reported that a nearly 3-year lead time can manifest between the onset of ED and CV events, which importantly would allow, if recognised, a window for risk modification and hopefully mitigate the likelihood of a CV event. The remainder of this chapter will explore this relationship from the perspective of epidemiology, shared pathophysiology and consideration of the predictive value of ED for CV risk assessment.

## 2.2 Epidemiological Studies Linking ED to CV Risk

Numerous epidemiological studies have supported a link between ED and CVD, as well as ED and the risk of CVD (Table 2.2). These studies included data from the general population, as well as cohorts of patients with diabetes or other conditions where CVD and ED are common. Importantly, these data suggest not only that ED and CVD are associated conditions but also that ED is linked to the risk of CVD.

An analysis of 300 consecutive patients with acute chest pain and angiographically confirmed coronary artery disease (CAD) found a 49% prevalence of ED in this population, with no significant difference in angiographic characteristics or clinical

**Table 2.2** Summary of prospective studies evaluating the link between erectile dysfunction and cardiovascular risk or cardiovascular events

| Author and date | Population | Follow-up | Outcomes | HR (95% CI) |
|---|---|---|---|---|
| Thompson et al. [24] | Men aged >55 years in the placebo group of the prostate cancer prevention trial ($n$ = 9457) | 7 years | First CV event | 1.45 (1.25–1.69)[a] |
| Schouten et al. [34] | Men aged 50–75 years without a known history of CVD ($n$ = 1248) | 6.33 years | CV events (acute MI, sudden death or stroke) | 2.6 (1.3–5.2)[a] |
| Gazzaruso et al.[35] | Men with T2DM and silent CAD ($n$ = 291) | 47.2 months | Deaths due to CAD, CHF or sudden death; nonfatal MI, unstable angina, need for repeat revascularisation, stroke or TIA, and symptomatic PAD | 2.1 (1.6–2.6)[a] |
| Inman et al.[36] | Men aged 40–79 years in the Olmsted County study of urinary symptoms and health status among men | 10 years | Angiographically diagnosed CAD, MI, sudden cardiac death | 1.8 (1.2–2.6)[a] |
| Banks et al.[26] | Men aged ≥45 years ($n$ = 95,037) | 1.9 years (hospitalisation) and 2.2 years (mortality) | CV events or deaths with or without a known history of CVD | CV events without CVD history: 1.35 (1.19–1.53)[a] CV events with a known CVD history: 2.37 (1.87–3.01)[a] |

Adapted from Gandaglia et al. [31]
Abbreviations: *CAD* coronary artery disease, *CHF* congestive heart failure, *CV* cardiovascular, *CVD* cardiovascular disease, *HR* hazard ratio, *MI* myocardial infarction, *PAD* peripheral artery disease, *T2DM* type 2 diabetes mellitus, *TIA* transient ischaemic attack
[a] Statistically significant ($P < 0.05$)

characteristics between those with and without ED [10]. However, in those with ED, it was reported that 67% of patients experienced ED symptoms prior to any CAD symptoms. The mean period of time between ED and CAD symptom onset was 38.8 months (range 1–168 months). The study also found that in patients with ED and type 1 diabetes mellitus, the development of sexual dysfunction preceded the onset of CAD in all patients. These findings suggest that not only is ED strongly associated with CAD but that symptoms of ED also tend to precede those of CAD, often years

prior to the onset of other CV manifestations. The lack of differences between those with and without ED highlights the vulnerability of penile arteries to disease, leading to the onset of ED before the development of other imaging or clinical markers [10]. The small size of the cavernosal arteries relative to the coronary vessels and the high demand for rapid and dramatic vasodilation of the cavernosal vascular bed allows for the recognition by the host of suboptimal responses within the penile circulation, typically years prior to coronary symptoms [42].

Other studies also suggest that ED and CVD are not only associated but that ED is an independent marker of future CV events. For instance, a longitudinal assessment of 9500 men in the United States Prostate Cancer Prevention Trial found that men with incident ED had higher risks of CV events [24]. The onset of CAD in a sample of 285 men with ED and CAD at baseline suggested that ED preceded the onset of CAD by approximately 2–3 years [25]. Other research also suggested that ED is predictive of subsequent CV events and CV mortality, even when controlling for other risk factors [26, 27]. Data from prospective studies examining the link between ED and CVD are summarised in Table 2.2.

The link between ED and future CV events has also been explored in a number of meta-analyses. For instance, a meta-analysis of seven cohort studies (including 45,558 men) found that ED was associated with 1.41 times higher risk of CVD, 1.23 times higher risk of all-cause mortality and 1.43 times higher risk of myocardial infarction compared to men without ED [28]. A meta-analysis of 16 published studies (including 92,757 men) found that ED increases the risk of future CV events by 44%, with a 62% increased risk for myocardial infarction and 39% increased risk for cerebrovascular events, while increasing the risk of all-cause mortality by 25% over a mean period of 6.1 years of follow-up [29]. In addition, a recent large retrospective cohort study of 430,261 men found that ED was associated with a higher rate of major adverse CV events (MACE) (8.94%) as compared with men without ED (4.58%) [30]. Therefore, a large body of data supports a link between ED and CVD while also highlighting that ED is often a precursor to CVD, increasing the risk of CVD compared with men without ED.

Overall, analyses have suggested that ED can precede the onset of CVD by approximately 2–5 years [31]. This is an important observation because the presence of ED at an earlier stage than other manifestations of CVD may be indicative of the presence of subclinical disease and/or CV risk factors that could have an impact on future health [8]. Indeed, a meta-analysis of studies evaluating the link between ED and subclinical CVD found that ED was consistently associated with endothelial dysfunction (measured by flow-mediated dilation) and carotid intima-media thickness [32]. Furthermore, ED has been linked with an increase in high-sensitivity troponin levels, a biomarker for future CV risk, as well as future CV mortality [33]. Therefore, ED appears to be linked to a high risk of CV events in the future. The critical clinical takeaway message is that, particularly for a younger man (<50 years) with arteriogenic ED, it should be considered a risk factor for CVD until proven otherwise [45].

In summary, the evidence to date strongly supports an association between ED and CVD in men. Importantly, ED is frequently seen in men without overt CVD or

with subclinical disease and has been associated with an increased risk of future CV events and mortality. These findings collectively suggest that ED may be an important early marker of CVD, highlighting the importance of CV risk factors in causing ED and CVD. The following section considers the pathophysiological mechanisms connecting ED and CVD in order to explore this association further and to support a role for ED as an early marker of CVD.

## 2.3 Shared Pathophysiological Mechanisms Between ED and CVD

The pathophysiology of ED is complex but is strongly linked to arterial flow in the corpora cavernosa [23]. Specifically, vasculogenic erectile function is facilitated through a combination of arterial dilation, sinusoid relaxation and venous compression in the penis [23]. Risk factors for ED and CVD may affect blood vessels, resulting in endothelial dysfunction, thickening of the tunica media and flow-limiting stenosis [8, 37], reflecting both functional and structural changes.

Endothelial dysfunction is a term that indicates an altered responsiveness of the endothelium to vasoactive stimuli and has been termed the 'common denominator' for ED and CVD [38]. Functional changes in arteries subsequent to CV risk factors lead to endothelial dysfunction, reductions in endothelium-mediated relaxations and reduced vasodilation of blood vessels [37]. Specific changes in endothelial function observed in people with ED include a reduction in endothelial nitric oxide synthase (eNOS) availability, reduced responsiveness to NO-mediated vasodilation and increased responsiveness to vasoconstrictive factors [21]. Other functional changes in the endothelium have been noted and include an increase in the expression of adhesion molecules, the release of pro-inflammatory factors, altered expression of growth factors and cytokines and the production of reactive oxygen species, all of which are detrimental to vasodilation in normal erectile function [21].

Structural changes are important mediators of CVD and ED and include arterial wall thickening and stenotic changes in arteries, whereby inflammatory reactions and atherosclerotic plaques reduced the effective lumen size for arterial blood flow [39]. Numerous CV risk factors are linked to atherosclerotic changes and arterial stiffness, including dyslipidaemia and smoking [40]. Over time, structural changes combined with functional changes in penile arteries reduce the potential for effective vasodilation, with reduced blood flow to the penile tissues and ED as a consequence [21]. A summary of the shared pathophysiological mechanisms seen in ED and CVD is presented in Fig. 2.1.

ED and CVD can be considered different manifestations of the same spectrum of disease [41] based on the degree to which risk factors overlap and endothelial dysfunction contributes to pathogenesis. The potential for ED to serve as a precursor of CV events or an early marker of CV risk may be explained by a number of mechanisms. One major conjecture is the artery size hypothesis [42]. Importantly, manifestations of CVD often present first in blood vessels with the smallest diameters, reflecting a vulnerability of these vessels to critical atherosclerosis and

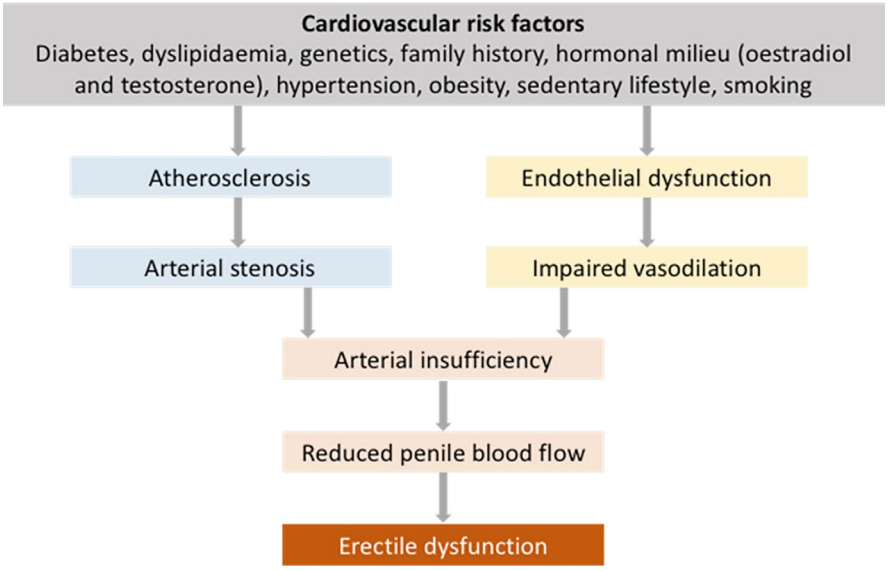


**Fig. 2.1** Overview of the pathophysiological links between cardiovascular disease and erectile dysfunction. This figure illustrates the role of cardiovascular risk factors in increasing the risk of structural arterial changes (atherosclerosis and arterial stenosis) and functional arterial changes (endothelial dysfunction and impaired vasodilation), resulting in arterial insufficiency, reduced penile blood flow and the symptoms of erectile dysfunction. (Adapted from reference [46])

other mechanisms [42]. While the coronary arteries are a good example of smaller vessel disease leading to CVD manifestations, such as myocardial infarction, smaller blood vessels in the corpora cavernosa may be more susceptible to endothelial damage [31]. Penile arteries are typically 1–2 mm in diameter, as compared with coronary arteries, which are 3–4 mm, and carotid arteries, which are 5–7 mm in diameter [36]. Accordingly, a lower burden of atherosclerosis is needed to result in the occlusion of the artery lumen in smaller vessels, making penile vessels susceptible to disease.

Another hypothesis suggests that older patients, who are at higher risk of both ED and CVD, exhibit arterial stiffness, which increases systolic and decreases diastolic blood pressure [39]. The stiffness of large arteries accompanied by systolic hypertension can cause pressure waves in smaller-diameter arteries, including penile arteries, increasing the risk of atherosclerosis in these vessels [5, 43]. Other mechanisms include changes in eNOS production, resulting in endothelial dysfunction and atherosclerosis, and the potential for chronic hypoxaemia stimuli to increase vasomotor tone, stimulate vascular growth factor production and increase vasoconstriction of arterioles [5]. Indeed, obstructive sleep apnoea is a condition characterised by the potential for hypoxaemia and is associated with CV risk factors and ED [44].

Therefore, symptoms of ED may be an early indicator of ongoing endothelial damage in other vasculature (e.g. coronary arteries), preceding symptoms of wider

CVD [45]. The implications of the role of ED as an early marker of CVD are considered in the following section, with a focus on the predictive value of ED when assessing CV risk in men.

## 2.4 The Predictive Value of ED in Assessing CV Risk

The assessment of CV risk is an important part of preventative medicine [47]. The Framingham studies provided an important development in identifying risk factors for CVD and highlighted how they may be considered collectively for an individual patient in the prediction of MACE [48, 49]. Consideration of the 'global' CV risk of a patient, rather than the presence of single risk factors, led to the implementation of risk models, calculators and scores. These approaches tend to consider the most common CV risk factors identified in epidemiological studies, including age, sex assigned at birth, hypertension, dyslipidaemia, diabetes mellitus and smoking, with some variation depending on the specific model or risk calculator employed [47]. Prospective studies have provided support for these strategies in estimating absolute or relative risk of MACE and in guiding risk stratification of patients as low, intermediate or high risk, which provides a basis for targeted lifestyle recommendation and pharmacological therapy [50–53].

Despite the widespread use of these tools and their value in risk stratification, they are associated with some important limitations. Firstly, these tools tend to have validity only when used in populations with the same features as the cohort in which they were validated, often reducing their accuracy for use in younger or older cohorts and in ethnic minority groups [5, 54]. Secondly, the tools often do not take into account the lifetime risk of CV events but provide risk over a typical period of 10 years, with age being weighted as one of the most important determinants of risk [5]. Consequently, younger patients (e.g. men aged $\leq$40 years) are often not classified as having a high risk of MACE, even in the presence of multiple risk factors. Another limitation is the use of a limited number of CV risk factors within these tools, which may improve the feasibility of implementation in practice but can reduce the sensitivity of risk estimation in a proportion of patients [55].

A proportion of patients classified as low or intermediate risk for MACE using these tools still experience a significant number of events. This likely reflects, at least in part, the effect of risk factors that are not included in common risk models and calculators [5]. The inclusion of other risk factors has been proposed as a means of reducing the 'residual risk' of CV events, particularly in specific patient populations (e.g. younger patients, those without traditional risk factors and those with risk levels at the threshold of treatment) [56]. For instance, the Joint British Societies 3 Board risk calculator includes risk factors that may be excluded from other calculators (e.g. body mass index, family history of CVD) and reduces the influence of age and gender on risk, which can be estimated across the lifetime of the individual [57]. While wider validation of this calculator is needed across populations, there is a growing emphasis on improving CV risk estimation by refining tools, including exploring the integration of additional risk factors and biomarkers into these tools.

Overall, there is a clear need for CV risk estimation to overcome the limitations of adopting a small number of risk factors that may underestimate risk in many populations while emphasising the need for an early marker of risk [41]. The role of ED in this context has been recognised as potentially valuable in refining risk estimation and adding to existing tools, based on its emergence as a unique early feature within the spectrum of CVD pathophysiology.

The importance of ED as a predictor of CV events has been explored in some studies, emphasising the value of ED as an early marker for CVD. As noted in Table 2.2, data indicate that the risk of CV events in patients with ED is increased as compared with men without ED. Therefore, the potential to screen for CVD and CV risk factors in men presenting with ED could have value in practice and has been explored in a number of studies. One modelling study found that screening for CVD in men with ED is cost-effective for the secondary prevention of CVD [58]. Furthermore, the screening of men with ED, regardless of severity, was associated with a substantial reduction in CVD events over 10 years and was shown to be cost-effective over this time period in a modelling study conducted in the Swiss population [59].

The inclusion of ED within routine CV screening tools or risk assessments also requires consideration. The QRISK3 calculator has incorporated ED diagnosis or treatment in men as a variable for CV risk estimation, reflecting the potential importance of this feature in enhancing risk estimation [60]. However, the inclusion of ED in this score is binary and does not consider the severity of ED, which may be a potential limitation in risk stratification [26, 60]. Indeed, the severity of ED has been linked to CV risk and outcomes in a meta-analysis of 25 studies (154,794 patients), where it was found that severe ED was associated with a higher risk of CVD and all-cause mortality compared to mild or moderate ED [61]. Evidence suggests that available risk scores may reliably identify patients with arteriogenic ED, making this a simple marker to evaluate in practice [45]. Therefore, the severity of ED may be an important aspect to include in clinical risk scoring for CVD.

When ED associated with vascular causes is identified in a patient, ED may be considered a potential risk factor for CVD. The presence of ED in this context should prompt a careful assessment of additional CV risk factors and initiation of preventative strategies against MACE. It is recommended that a formal CV risk score be applied in these patients, supplemented with a detailed clinical history, physical examination, assessment of the severity and duration of ED, fasting plasma glucose assessment, electrocardiography, measurement of serum creatinine and albumin:creatinine ratio, assessment of plasma lipid profile and evaluation of MetS [5]. Total testosterone levels should also be assessed as a potential cause of ED, which may prompt testosterone therapy [5]. Referral to a cardiologist should be considered in men with ED and a high CV risk, while additional testing may be indicated in those with intermediate CV risk.

The Princeton III Consensus (Expert Panel) guidelines, published in 2012, advocated for exercise stress testing, the assessment of carotid intima-media thickness and the non-invasive assessment of endothelial function to guide CV risk assessment in patients with ED [47]. Recently, the Princeton IV Consensus (Expert Panel)

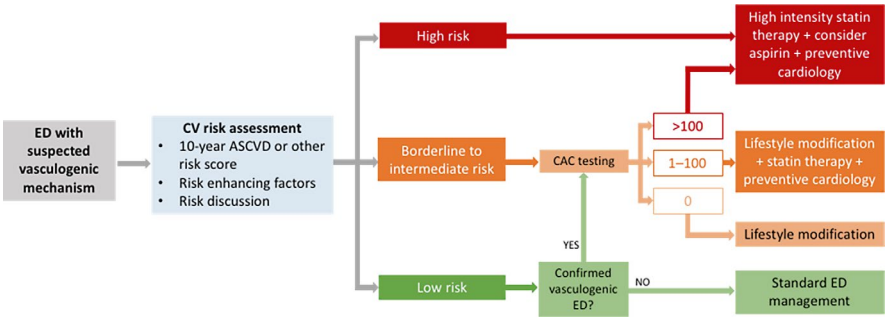


**Fig. 2.2** Illustration of how erectile dysfunction may prompt cardiovascular risk assessment. A patient with suspected vasculogenic erectile dysfunction (ED) should undergo a cardiovascular (CV) risk assessment incorporating a 10-year atherosclerotic cardiovascular disease (AVSCD) risk scoring (or the use of a similar score). (Kloner et al. [31]; Arnett et al. [63])

guidelines [62] updated these recommendations, emphasising the importance of considering men with ED as at high risk of CVD until proven otherwise. In this Expert Panel Consensus, it is recommended that CV risk scoring should be performed using the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) atherosclerotic CVD (ASCVD) risk score for all men with predominantly vasculogenic ED [63]. This score relies on traditional risk factors for CVD, and therefore, augmentation is recommended in younger men (aged 40–60 years) with vasculogenic ED and borderline/intermediate risk (5–20%), as this group may have their risk underestimated [64]. Coronary artery calcium measurement has subsequently been introduced as a routine evaluation that can enhance CV risk assessment in this cohort and may have value in improving risk estimation [62, 65]. Following these assessments, CAC scores may be used to guide the need for lifestyle interventions, statin therapy, aspirin use and other interventions, along with referral to cardiologists in those with high risk of CV events [62].

There remains some uncertainty over the optimal sequence of tests and the superiority of one test over another in CV risk prognostication. In addition, other risk scores may also be preferred for populations outside of the United States, where the ASCVD was validated [66]. A pragmatic strategy aligned with available guidance is presented in Fig. 2.2 for supporting CV risk assessment in men presenting with ED.

## 2.5 Conclusions: The Role of ED Assessment in Routine CV Health Screenings

CVD is a common cause of morbidity and mortality in men, particularly among older age groups. A constellation of risk factors has been clearly linked to CVD and future CV risk, including lifestyle risk factors. However, at present, there is no perfect single marker that is predictive of future CV risk. The importance of preventative strategies in mitigating the risk of future CVD events, including myocardial

infarction and stroke, highlights the need for improvements in risk prediction. In particular, there is a need to establish early markers for CVD to maximise opportunities for prevention.

This chapter reviews the existing medical literature and supportive evidence for the inclusion of ED assessment as part of routine CV health screenings, with ED serving as a valuable marker for future CV risk in men. ED is a condition that strongly reflects risk factors for CVD and is predictive of CVD, presenting years prior to the onset of most common CVD manifestations. In ageing men, ED should be considered a potentially valuable marker of future CV risk and should be routinely included in CV health screenings. In patients with CV symptoms or pre-existing CV conditions, sexual function screening should be performed, including an evaluation of erectile function. This may include the use of validated questionnaires to assess ED, such as the brief version of the International Index of Erectile Function-5 (IIEF-5) [29]. The assessment of ED should prompt a wider evaluation of lifestyle risk factors and comorbidities that may contribute to poor outcomes, providing an opportunity for targeted lifestyle advice and interventions [62]. This may also include an evaluation of non-traditional risk factors for CVD, such as metabolic or hormonal profiles, ED severity, penile artery flow characteristics and psychological factors [5].

The diagnosis of ED should be followed by detailed sexual health assessment, counselling, shared decision-making and appropriate interventions, such as phosphodiesterase type 5 inhibitor (PDE5i) therapy [66]. The benefits of PDE5i therapy have been observed in improving ED symptoms and subsequent sexual activity levels and also in providing cardioprotective effects [67, 68]. These observations are largely based on retrospective studies and may be influenced by confounding factors, such as increased levels of sexual activity rather than the pharmacological effects of PDE5is, accounting for improvement in CV risk [62]. However, evidence suggesting the dose-dependent effects of PDE5i therapy on adverse CV outcomes, as well as the absence of CV risk reduction from other pharmacotherapies that improve sexual activity (e.g. alprostadil), is suggestive of direct CV benefits from PDE5is [62, 69]. Therefore, the early identification of vasculogenic ED and the recognition that its onset can be considered an early signal of CVD, leading to risk reduction therapy and appropriate management with PDE5is, may have positive effects on future CV risk, which should be explored further in prospective studies.

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# Glycaemic Control and Erectile Function: Unravelling the Links to Type 2 Diabetes Mellitus

3

Giovanni Corona and Yacov Reisman [Cobi]

**Abstract**

Type 2 diabetes mellitus (T2DM) is a common non-communicable disease that is associated with a high morbidity and mortality burden in patients, largely due to cardiovascular disease (CVD). There is a high prevalence of erectile dysfunction (ED) in men with T2DM across global populations. This reflects the links between ED and CVD, as well as shared risk factors for CVD and T2DM, where ED may serve as an early marker for disease. This chapter examines the biochemical and physiological connections between glycaemic control and erectile function and the importance of chronic hyperglycaemia in driving neurological and vascular mechanisms associated with the development of ED. There is a complex interplay between cardiovascular risk factors, comorbidities, hyperglycaemia and endothelial dysfunction in patients with ED, which is important when guiding patient care. The relevance of ED as an early marker for T2DM is considered in light of this complex dynamic, providing a basis for using ED as an opportunity to screen for hyperglycaemia and associated risk factors/comorbidities. Furthermore, the importance of considering ED in patients with T2DM is emphasised, summarizing recent guidelines and providing expert insights into how ED evaluation may be integrated into T2DM care processes.

**Keywords**

Diabetes · Glycaemic control · Erectile dysfunction · Screening · Management

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## 3.1 The Prevalence of Erectile Dysfunction in Men with Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is one of the most common non-communicable diseases affecting the global population [1]. The condition is characterized by persistent hyperglycaemia, which is associated with a risk of complications that have an impact on morbidity and mortality [2]. The Global Burden of Disease Study estimated that the total number of people affected by diabetes was 529 million in 2021, with 96.0% of cases attributed to T2DM [1]. The burden of T2DM is higher in males than in females, and prevalence increases with age [1]. Patients with T2DM have nearly doubled the risk of premature death and a substantial reduction in life expectancy compared with the population without T2DM [3].

Cardiovascular disease (CVD) is a leading cause of mortality in patients with T2DM, with the risk of cardiovascular (CV) events linked to poor glycaemic control [4]. Persistent hyperglycaemia is associated with the risk of microvascular and macrovascular complications, including coronary heart disease, stroke, heart failure, peripheral vascular disease, retinopathy and neuropathy [5]. Furthermore, the risk factors for developing T2DM include both genetic and environmental components but largely reflect those associated with CVD, including lifestyle factors such as overweight/obesity (especially visceral obesity), physical inactivity, smoking and dietary habits [6]. Consequently, T2DM and CVD are closely related and often co-occur in patients.

As noted in the previous chapter, there is a substantial body of evidence supporting an association between erectile dysfunction (ED) and CV risk factors, with ED emerging as a potential early marker for CVD [7–9]. The close association between CVD and T2DM suggests that ED may also have the potential to serve as an early marker for T2DM [10, 11]. Furthermore, the independent effects of the pathophysiological processes seen in T2DM may be associated with a risk for ED, necessitating an examination of how ED and T2DM may be linked in the clinical population [12].

Numerous epidemiological studies have demonstrated that there is a high prevalence of ED in men with a diagnosis of T2DM. Prevalence estimates vary, but up to 90% of men with T2DM may be affected by ED—the variability can be accounted for using the methods to define ED and the characteristics of the population assessed [13, 14]. However, there is a consistent association between ED and T2DM noted in the literature (Table 3.1). For instance, in an evaluation of 31,027 men aged 53–90 years in the Health Professionals Follow-Up Study cohort, the prevalence of ED among men with diabetes was 45.8% versus 24.1% in those without diabetes [15]. In men with T2DM, the risk of ED was shown to increase with the duration of T2DM [15]. Another study in a population of 9868 men with diabetes found that the prevalence of ED was 37% [16]. An evaluation of 1118 Japanese men undergoing treatment for T2DM demonstrated a prevalence of ED of 90% [17]. More recently, one study found that ED affected 59.38% of men with T2DM in a population derived from a tertiary care centre cohort in India [14].

**Table 3.1** Epidemiology of erectile dysfunction in men with diabetes mellitus across global populations

| Author and date | Country | Participants, *N* | Prevalence of erectile dysfunction, % |
|---|---|---|---|
| Fedele et al. [16] | Italy | 9868 | 37 |
| Bacon et al. [15] | USA | 2108 | 45.8 |
| Roth et al. [28] | Israel | 1412 | 65.5 |
| Cho et al. [29] | South Korea | 1312 | 65.4 |
| Ma et al. [30] | China | 2306 | 26.7 |
| Batty et al. [31] | UK | 6304 | 50.1 |
| Wang et al. [32] | Canada | 1466 | 26.2 |
| Corona et al. [33] | Italy | 1503 | 66.8 |
| Tridiantari et al. [34] | Indonesia | 122 | 84.4 |
| Parmar et al. [14] | India | 357 | 59.4 |

Abbreviations: UK, United Kingdom; USA, United States of America

Similar patterns have been reported worldwide, with international studies suggesting that men with T2DM across the globe have a consistently high risk of ED. A meta-analysis of 70 studies conducted across multiple nations and regions found that the prevalence of ED was 66.3% among men with a diagnosis of T2DM [18]. Another meta-analysis of 13 studies originating from Africa found that the prevalence of ED was 71.45% in men with T2DM [19]. Studies in European and Asian men suggest that the presence of T2DM is associated with an increased risk of ED compared to men without a diagnosis of T2DM [20].

Further data suggest that the risk of having ED is increased in men with T2DM compared with healthy controls. One meta-analysis showed that men with diabetes have approximately 3.5 times higher risk of ED than men without diabetes [18]. Data from the Massachusetts Male Aging Study found that the age-adjusted probability of ED was three times greater in patients with diabetes than in those without diabetes [21]. The Health Professionals Follow-Up Study cohort found that men with T2DM had a higher risk of ED (relative risk 1.3; 95% confidence interval (CI), 1.1–1.5) compared with men without T2DM. This risk may be increased in men with a longer duration of T2DM and in those with CV conditions or risk factors compared with the population without T2DM [15, 18].

The importance of ED in patients with T2DM reflects its association with quality of life, morbidity and mortality. It has been shown that quality of life is more likely to be impaired when ED is present in men with T2DM [22, 23]. Furthermore, the presence of ED is associated with an increased risk of CV events in men with T2DM compared with men without ED [24, 25]. Men with T2DM also represent a group in which the management of ED may be particularly challenging due to lower response rates to pharmacological therapies than in men without T2DM [26, 27].

In summary, epidemiological data support a link between ED and T2DM, suggesting that these two conditions are interrelated. This is an important association, particularly as the presence of ED may be linked to poorer quality of life, greater morbidity and higher mortality risk than that seen in T2DM where ED is not present. The following section considers the biochemical and physiological factors that

account for this association, setting the scene for an exploration of the mechanisms linking hyperglycaemia and ED and the potential for ED to serve as an early marker for T2DM.

## 3.2 Biochemical and Physiological Connections Between Poor Glycaemic Control and Erectile Function

The characteristic pathophysiological mechanism accounting for the risk of complications in T2DM is hyperglycaemia [2]. Poor glycaemic control emerges as a consequence of reduced effects of insulin, largely due to the development of insulin resistance [35]. A complex range of factors contribute to the perpetuation of insulin resistance in T2DM, including the influence of gut dysbiosis, inflammation, reactive oxygen species (ROS) and pancreatic beta-cell dysfunction [2]. Over time, beta-cell dysfunction leads to a reduction in secreted insulin, and insulin resistance contributes to sustained elevated blood glucose levels, resulting in the progression of T2DM [2].

Importantly, there is a link between poor glycaemic control/hyperglycaemia and the risk of ED in men with T2DM [36]. In an analysis of five studies exploring the association between hyperglycaemia and ED risk in T2DM, three reported a significant association between these factors, while the remaining studies showed a weak correlation or borderline significant correlation [36]. A study of 78 men with T2DM found that the mean erectile function score decreased as levels of glycated haemoglobin (HbA1c) increased ($P = 0.002$), with multivariate analysis demonstrating that HbA1c was an independent predictor for erectile function ($P < 0.001$) [37]. A study in 555 men with T2DM similarly found that the mean HbA1c level was significantly higher in men with ED than in those without ED ($P = 0.01$) [38]. Another study of 1312 men with T2DM showed that the severity of ED was linked to fasting glucose levels ($P < 0.05$) and HbA1c levels ($P < 0.001$) [29], while a study of 792 men with T2DM also suggested that mean HbA1c levels were higher in men aged <60 years with severe ED compared with those without severe ED ($P = 0.0002$) [39].

The role of glycaemic control in erectile function is likely complex and reflects the range of effects that hyperglycaemia has on normal biochemical and physiological processes. The pathogenesis of ED is strongly linked to the disruption of the vascular function of penile tissues, which reflects the impact of endothelial dysfunction [40]. Endothelial dysfunction is seen in patients with T2DM and reflects a range of pathological processes, including the effects of hyperglycaemia [12]. In addition, normal erectile function is associated with neurological mechanisms, through which parasympathetic stimulation results in the induction of an erection, while sympathetic pathways are linked to detumescence [40]. Importantly, the pathophysiology of T2DM is associated with the disruption of normal vascular and neurological function, largely governed by the effects of hyperglycaemia, connecting a hyperglycaemic state to key mechanisms responsible for the development of ED [2].

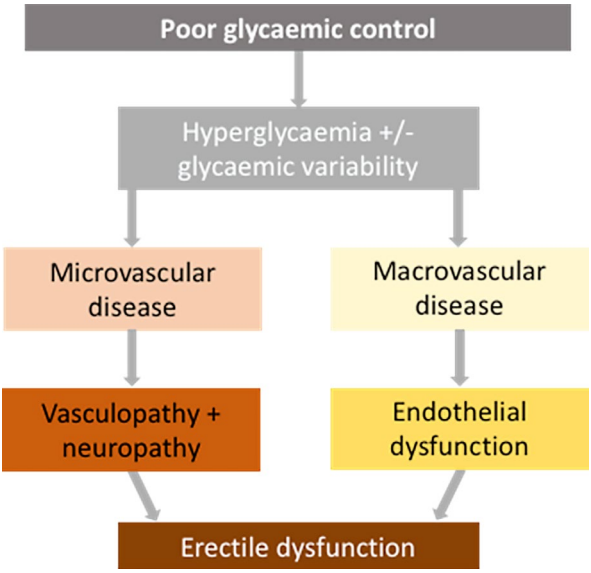


**Fig. 3.1** Overview of the mechanisms linking poor glycaemic control and erectile dysfunction. This figure illustrates the connection between poor glycaemic control characterised by both chronic hyperglycaemia and glycaemic variability. Both manifestations may contribute to macrovascular and microvascular disease, leading to vasculopathy, neuropathy, endothelial dysfunction and erectile dysfunction [42, 46, 47]

A summary of the key mechanisms linking poor glycaemic control and ED is presented in Fig. 3.1. Importantly, hyperglycaemia in T2DM is associated with a risk for both macrovascular and microvascular complications [2]. Macrovascular complications include those linked to CV events, such as stroke and myocardial infarction [41]. Specifically, diabetic macroangiopathy comprises both direct endothelial injury and the effects of atherosclerosis, increasing the risk of arterial lumen occlusion and associated vascular events [42]. In principle, this macrovascular mechanism may directly affect penile arteries, reducing effective blood flow and endothelial responsiveness, thereby decreasing the potential for successful erection. Microangiopathy associated with diabetes includes endothelial injury, thickening of the basement membrane, erythrocyte and platelet adhesion, and the risk of microthrombi in the small vessels [43]. Microvascular complications of T2DM, associated with hyperglycaemia, may reduce the perfusion of nerves, leading to an increased risk of ischaemia and reduced neuronal function [44]. Autonomic and peripheral nerve dysfunction is commonly seen in patients with T2DM and has been linked to hyperglycaemia [45].

Many of the effects of poor glycaemic control observed on macro- and microvascular disease are reflective of the chronic or persistent effects of hyperglycaemia over time, with many complications emerging years after the diagnosis of T2DM [42]. However, fluctuations in glycaemic control have been shown to activate oxidative stress pathways, promote endothelial dysfunction and promote inflammatory responses in tissues [46]. Glycaemic variability in patients with chronic hyperglycaemia can exacerbate the biochemical and physiological mechanisms linked to macro- and microvascular disease, increasing the risks of complications [46, 47]. More research is needed to confirm the importance of glycaemic variability, specifically in the context of ED development.

Independent predictors of ED in men with T2DM, apart from hyperglycaemia, include autonomic neuropathy, testosterone deficiency and obesity [1, 8, 45, 48–51]. These factors and others may play a role in contributing to the risk of ED and are considered in the following section, with a focus on their role and their interactions with chronic hyperglycaemia as a driver of ED.

## 3.3 Impact of Chronic Hyperglycaemia on Vascular and Neurological Systems Pertinent to Erectile Capability

It is widely recognised that both vascular and neurological factors play an important role in the pathophysiology of ED [52]. As noted in the previous section, T2DM is linked to biochemical and physiological evidence of vascular dysfunction and neurological disease, both of which increase the risk of ED. Importantly, persistent hyperglycaemia is a key driver of T2DM-related vascular and neurological disease. The effects of hyperglycaemia over the chronic course of disease on neurological and vascular systems is summarised in Fig. 3.2.

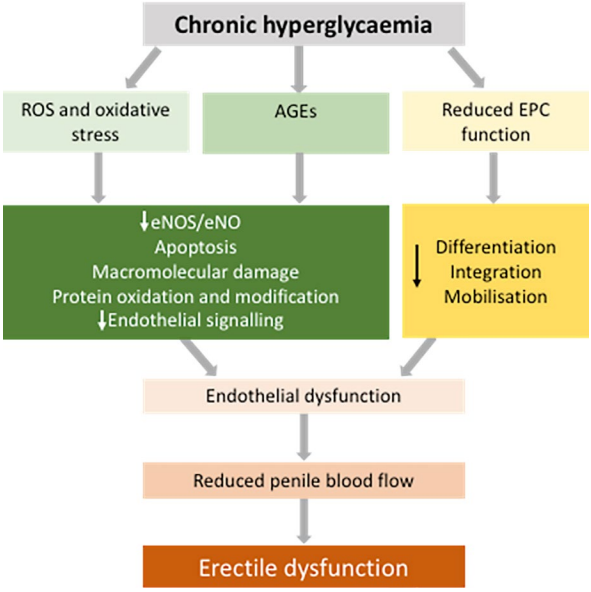


**Fig. 3.2** The role of chronic hyperglycaemia in the development of erectile dysfunction. The figure illustrates the impact of chronic hyperglycaemia on reactive oxygen species (ROS) production and oxidative stress, advanced glycation end products (AGEs) and endothelial progenitor cell (EPC) function. Both oxidative stress and AGEs result in molecular changes that promote endothelial dysfunction. Reduced EPC function also causes a reduction in endothelial health [53, 56, 57]. Abbreviations: *AGE* advanced glycation end product, *eNO* endothelial nitric oxide, *eNOS* endothelial nitric oxide synthase, *EPC* endothelial progenitor cell, *ROS* reactive oxygen species

Chronic hyperglycaemia is associated with direct effects on tissues, including the generation of advanced glycation end products (AGEs) [53]. In addition, hyperglycaemia is associated with oxidative stress through the generation of reactive oxygen species (ROS), which are considered key factors in the development of ED [54]. Together, AGEs and oxidative stress promote molecular changes in the vascular endothelium, which can increase the risk of endothelial dysfunction [55]. These changes include a reduction in the bioavailability of endothelial nitric oxide (eNO) and endothelial nitric oxide synthase (eNOS), reducing the potential for smooth muscle relaxation and vasodilation, as well as apoptosis, protein oxidation and reduction in vascular endothelial signalling [55, 56], which are essential for erectile function. Structural changes may also be associated with the effects of hyperglycaemia, including an increased risk of thrombosis and vasoconstriction secondary to atherosclerosis and inflammation [57]. In penile arteries affected by endothelial dysfunction and structural pathology, there is a reduced potential for successful or sustained erection because of impaired vasodilation and blood entry into the penile tissues [57].

Hyperglycaemia may lead to an imbalance between the mechanisms driving endothelial dysfunction and those that support endothelial repair. The role of endothelial progenitor cells (EPCs) in the pathogenesis of T2DM has also been described [56]. It is recognised that EPCs play an important role in angiogenesis and vasculogenesis, providing a response to endothelial injury that maintains endothelial function [58]. However, in T2DM, the function of EPCs is reduced, characterised by poor mobilisation, differentiation and integration of these cells, resulting in reduced endothelial health [56]. Conversely, where glycaemic control is optimised, the function of EPCs is maintained, which encourages angiogenesis and re-endothelialisation of blood vessels and can improve endothelial health and function [59]. In addition to promoting pathological mechanisms responsible for poor endothelial function (e.g. AGEs, oxidative stress), the pathophysiology of T2DM also reduces the regenerative capacity of the endothelium through its effects on EPCs [56]. Importantly, the possibility of restoring EPC function as a strategy to improve endothelial health in patients with T2DM has been discussed, with potential beneficial effects seen with phosphodiesterase 5 inhibitor (PDE5i) therapies and testosterone replacement therapies, where indicated [56].

While hyperglycaemia is an important mechanism linked to the risk of ED in patients with T2DM, one cannot overlook the potential influence of additional comorbidities and risk factors for ED commonly seen in this population. Indeed, there is an interplay of CV risk factors, hyperglycaemia and endothelial dysfunction in normal and pathological erectile function [42]. Patients with T2DM typically exhibit a range of CV risk factors, including obesity, smoking, low physical activity levels and dyslipidaemia [12]. These risk factors have been associated with the incidence of ED across populations and may therefore play an important role in driving its development independent of glycaemic control [60, 61].

Many of the most common risk factors associated with ED are also implicated in the development of T2DM [42], including hypertension, CVD, obesity, low levels of physical activity, dyslipidaemia and smoking [62, 63]. These risk factors are

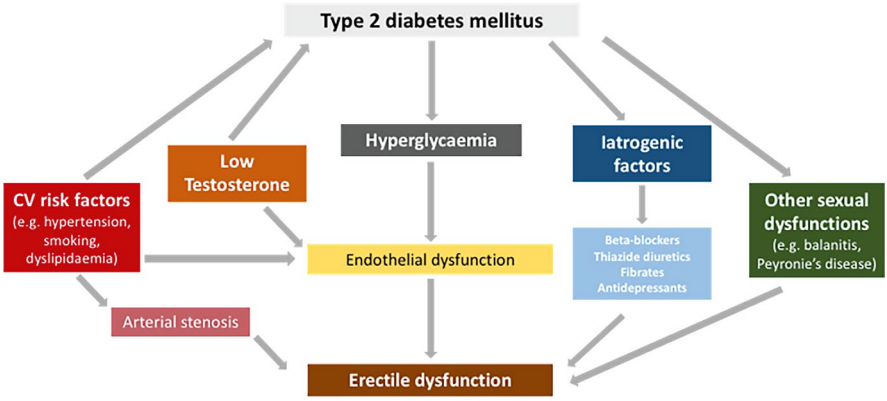


**Fig. 3.3** The complex interplay between cardiovascular risk factors, comorbidities, hyperglycaemia and endothelial dysfunction in the context of erectile dysfunction. This diagram illustrates the wide range of factors that may influence the potential for erectile dysfunction in patients with type 2 diabetes mellitus, including hyperglycaemia, low testosterone levels, cardiovascular risk factors and iatrogenic factors [8, 11, 49, 57]. Abbreviation: *CV* cardiovascular

associated with specific effects on endothelial function which can drive the risk of ED. For instance, hypertension is associated with an increased risk of arterial endothelial damage and irregular blood flow, resulting in arterial stiffening and an increased risk of lumen occlusion [64, 65]. Obesity is associated with an increased level of systemic inflammation, leading directly to endothelial dysfunction [66]. However, obesity may also drive insulin resistance and may play a role in the development of T2DM, providing a link between obesity and hyperglycaemia [67]. The metabolic syndrome components of visceral obesity, hypertension, dyslipidaemia insulin resistance and T2DM are associated with ED and should be assessed during sexual dysfunction workups [8, 68]. Hence, there is an evident overlap in risk factors between ED and T2DM, and the interactions between mechanisms driving ED may be extensive.

Other factors may also influence the development of ED in T2DM, interacting with the effects of hyperglycaemia either directly or indirectly (Fig. 3.3). The aetiology of ED is complex and includes a range of factors that influence neurological, vascular and psychological health [57]. Psychological health may be an important factor associated with ED in the population with T2DM. For instance, depression and low mood are commonly observed in patients with T2DM [69]. Depression symptoms are associated with a reduction in sexual function and libido in many patients, impacting the central mechanisms that may stimulate erectile function [69, 70]. In addition, patients with depression and low mood may have an increased risk of poor lifestyle choices, contributing to ED risk [71, 72]. The impact of medications used for the management of T2DM on ED risk has also been explored in the literature [41]. For instance, the use of beta blockers in patients with T2DM has been associated with an increased risk in ED [73, 74]. Similarly, the risk of ED may be elevated with thiazide diuretics, antidepressants and medications for neuropathic pain control, which are often used in patients with diabetes [73].

The role of comorbidities and complications may also be important in determining the risk of ED. For instance, there is a marked association between T2DM and low testosterone T (hypogonadism), with at least 25% of men demonstrating secondary hypogonadism and a further 4% with primary hypogonadism [75]. Low levels of T are associated with visceral obesity and metabolic syndrome and can lead to a reduction in libido and low mood [76], which can influence ED risk. Furthermore, low T levels can directly contribute to the impairment of endothelial function and hyperglycaemia, exacerbating mechanisms linked to ED development in patients with T2DM [8, 48, 49, 77, 78]. Complications of T2DM, including autonomic neuropathy and renal disease, have also been associated with an increased risk of ED [2, 79]. Therefore, a wide range of factors and a complex range of interactions may link T2DM and ED.

## 3.4 Erectile Dysfunction as a Potential Early Clinical Indicator of Undetected Type 2 Diabetes Mellitus

The previous section provides a clear insight into how the chronic state of hyperglycaemia seen in men with T2DM may be connected to pathophysiological mechanisms driving ED, potentially interacting with other risk factors and comorbidities commonly seen in association with T2DM. Importantly, evidence suggests that ED is not a late presentation of T2DM and is commonly seen in men with pre-diabetes or early stages of T2DM [10, 11, 80]. There is evidence for ED as an early marker of T2DM, and in many cases, ED may be the initial presenting symptom. As noted in the previous chapter discussing the links between ED and CVD [7, 81], there is the potential for ED to serve as an early marker of systemic illness, which may have important implications for patient screening, preventive interventions and active management. The role of ED as an early marker of T2DM is explored in this section.

It has been reported that ED is the first sign of T2DM in 12–15% of patients presenting to health services [82, 83]. There is also evidence supporting the presence of ED early in the disease process or prior to symptomatic T2DM. In a study of 1332 patients referred for ED, it was noted that ED was an early marker of endocrine and glycaemic disorders [10]. Specifically, the study showed that 17.3% of men with ED were diagnosed with new glycaemic disorders, including T2DM and pre-diabetes. Furthermore, the severity of ED was associated with the likelihood of a new diagnosis of T2DM [10]. Similar results have been reported by other authors [84].

A meta-analysis of nine cross-sectional or case-control studies found that there was a higher rate of ED in men with pre-diabetes compared with normoglycaemia (OR, 1.6; 95% CI, 1.28–2.07; $P < 0.001$). The findings also suggested that this association was not influenced by the definition of pre-diabetes or the tool used to diagnose ED, although the association was stronger in younger men (mean age < 50 years) [85].

A recent retrospective cohort study in men aged 18–40 years with ED but without evidence of pre-diabetes, hyperglycaemia or T2DM found that there was an

association between ED diagnosis and the risk of pre-diabetes/T2DM [12]. After controlling for confounders, it was found that ED diagnosis was associated with an increased risk of pre-diabetes/T2DM (relative risk, 1.34; 95%CI, 1.10–1.74). Furthermore, in patients who were diagnosed with ED, 36.3% were diagnosed with pre-diabetes/T2DM on the same day, while 73.7% were diagnosed with pre-diabetes/T2DM within 12 months of their ED diagnosis [12].

The value of ED as a marker of future T2DM was demonstrated in an 11-year population-based cohort study in a primary care setting [86]. This study found that men with ED (diagnosed using IIEF-5) but without a history of known T2DM showed a higher prevalence of undetected T2DM (OR, 4.7; 95%CI, 1.6–14.4) and pre-diabetes (OR, 1.9; 95%CI, 1.1–3.2) compared with men without a diagnosis of ED. The cumulative incidence of T2DM over 11 years of follow-up was higher among men with symptoms of ED at the start of the study [86].

It has been demonstrated that the risk of developing T2DM in association with ED is highest in men 45 years or younger, suggesting the potential value of ED as an early marker of T2DM [87]. Additionally, it was found that ED was more common in men with T2DM than in healthy men and that screening for ED before T2DM improves the accuracy of the Latin American version of the Finnish Diabetes Risk Score (LA-FINDRISC) for undiagnosed T2DM [88]. However, there remains a limited number of studies evaluating the value of ED as a means of screening for T2DM.

One of the leading explanations for ED as a putative marker for future risk of adverse health outcomes is the artery size hypothesis [89]. This hypothesis suggests that the smaller diameter of penile arteries compared with other arteries, including coronary vessels, provides a physiological basis for ED as an early marker of CVD [89]. Smaller-diameter arteries may be more vulnerable to impaired blood flow as a consequence of endothelial damage and arterial stenosis secondary to the effects of hyperglycaemia and atherosclerotic mechanisms, respectively [57]. Therefore, where these mechanisms are present in patients with pre-diabetes or early T2DM, the development of ED may precede other clinical signs and symptoms. The potential to use ED as a marker in screening for T2DM may have some clinical importance in facilitating earlier diagnosis and treatment.

## 3.5 Integrating Evaluation of Erectile Dysfunction into Diabetes Screening and Management Strategies

The presence of comorbid ED in men with T2DM is common and is associated with the risk for future CVD, highlighting the importance of evaluating ED within diabetes screening and management strategies [90]. The evaluation of ED as part of a routine diabetes screening process should be considered an important part of a comprehensive patient workup [8, 91, 92]. This is particularly important, given the occurrence of ED prior to overt signs of T2DM or as an early consequence of the disease process.

ED should also be evaluated during the follow-up of patients with T2DM due to the chronic nature of the condition and the association between ED risk and the duration of T2DM. Guidelines generally advocate for regular screening for ED in men with T2DM [8, 91, 92]. Annual assessments for ED during the course of diabetes follow-up should be a routine part of practice. The use of tools such as IIEF-5 may have value in diagnosing ED among men with T2DM [93]. These assessments also provide an opportunity for initiating or monitoring interventions for ED, which may improve patients' quality of life [8]. Optimal management should take into account the need for the pharmacological management of ED, including the use of PDE5is or T where indicated, as well as the management of lifestyle factors that can drive pathogenesis and the risk of poor outcomes [8].

Given the value of ED as an early marker of T2DM, it is important to recognise that the diagnosis of ED should prompt a detailed assessment of risk factors, including the presence of hyperglycaemic disorders [10]. Simple screening for hyperglycaemia may be routinely adopted in men with ED, which can prompt a diagnosis of pre-diabetes or T2DM [42]. However, some important barriers to effective implementation of guidance for ED and T2DM assessment should be considered. For instance, ED may be an early marker for T2DM, but this is only of value if men present to health services for the management of ED. It has been observed that men may be reluctant to discuss symptoms of ED with healthcare professionals, which potentially reduces opportunities for the early identification of this condition and for subsequent T2DM screening [94]. A systematic review found that men may experience embarrassment, helplessness, reluctance to seek help, financial constraints and negative experiences of healthcare professional interactions (e.g. dismissal of symptoms)—all of which reduce the potential to address ED associated with T2DM [95]. Furthermore, the availability of direct-to-consumer products for ED, including pharmacological therapies, reduces the motivation for men to seek professional advice [12, 96].

In order to overcome barriers to identifying and managing ED effectively, healthcare systems should focus on improving screening for ED, creating a more positive environment for discussing ED, encouraging healthcare professionals to engage in proactive discussions, and [95, 97]. These measures, combined with a heightened awareness of the link between ED and T2DM among healthcare professionals, may facilitate the earlier identification of these conditions, prompting more effective management and improved outcomes.

In conclusion, this chapter highlights the complexity of the links between T2DM and ED, considering the biochemical, physiological and pathological processes connecting these entities. Importantly, ED and T2DM often coexist in patients, representing an important clinical challenge in practice. The earlier identification of ED in men with T2DM, as well as the consideration of ED as an early marker of T2DM or insulin resistance, has the potential to improve the recognition and management of both conditions.

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# 4 Psychological and Psychiatric Underpinnings of Erectile Dysfunction: Anxiety, Depression and Stress as a Predictor of Men's Health

Tommaso B. Jannini and Annamaria Giraldi

**Abstract**

Phosphodiesterase type 5 inhibitor therapy has revolutionised the management of erectile dysfunction (ED). However, emphasis on the biological causes and treatment of ED may overlook the importance of psychological, psychiatric and relational/social factors associated with this symptom. This chapter explores the association between these factors and ED while highlighting the importance of the inter-relationships between psychological, psychiatric, relational/social and biological factors. The role of anxiety, depression and stress as a driver of hormonal changes that may lead to the development of ED is also considered. Notably, there is a correlation between psychological well-being and physical health outcomes, and ED may serve as an indicator of the risk of poor health. This has important implications for the management of ED, where psychological interventions such as cognitive-behavioural therapy may play an important role in improving outcomes. The implications of ED as a pre-emptive sign of potential mental health concerns are considered from a practice perspective, underlining the importance of screening for mental health problems or psychological symptoms in patients with ED.

**Keywords**

Psychological · Psychiatric · Erectile dysfunction · Stress · Anxiety · Depression

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## 4.1 Psychological Factors Contributing to the Onset of ED

Erectile dysfunction (ED) is a common sexual disorder in men associated with a dynamic interplay between hormonal, vascular, neurological, psychosocial and cultural factors [1]. The advent of phosphodiesterase type 5 inhibitors (PDE5is) undeniably revolutionised the potential to manage this condition, placing an important emphasis on the biological underpinnings of ED [2]. However, it has been argued that this has left the psychological, psychiatric and relational/social factors linked to ED underexplored [3]. Previous chapters in this series have considered the importance of cardiovascular disease and type 2 diabetes mellitus in relation to ED, highlighting the potential for ED to serve as an early marker for these conditions and associated risk factors. This chapter will attempt to highlight that psychological factors are important in the onset of ED and impact the well-being and outcomes of men (and their partners) who are affected. Rather than positioning these factors in opposition to biological factors linked to ED, a dichotomous approach is rejected in favour of a more nuanced appreciation of the integrated effects of biological and psychological factors on ED.

The history of how biology and psychology have influenced an understanding of the causes of ED and the treatment approaches that may be applied to the affected individual is complex and illustrates an alternating approach to biological or psychological management. Historically, ED has been understood and treated as a physical or spiritual ailment, with treatments including a variety of herbal remedies and preparations, as well as amulets and prayer [4]. This model persisted until the development of psychiatry as a discipline and an increasing emphasis on the psychological aspects of sexual functioning [3]. The influence of psychiatric factors was explored during the late nineteenth and early twentieth centuries when psychoanalysis became the mainstay of ED management [4]. The psychoanalytic approach to ED was pioneered by Freud and others, positing the root of sexual dysfunction as lying within the psyche of the individual. Thus, concepts such as the Oedipus complex and the stunted phasic development of sexual function were embedded within psychoanalytical perspectives on ED treatment for the first half of the twentieth century [4].

Following this period, psychological treatments focusing on cognitive-behavioural models were advanced by Masters and Johnson, representing the replacement of the psychiatrist with the psychologist in the management of conditions such as ED [3]. This period emphasised the importance of the biopsychosocial model within the context of sexual dysfunction, with sex therapy aiming to reduce negative cognitions [3, 4]. The dominance of sex therapy influenced by Masters and Johnson persisted for decades, emphasising the importance of relational and psychological factors in ED. However, in 1998, the paradigm shifted again, with the emergence of sildenafil (PDE5i) and an increased knowledge about physiological and biochemical mechanisms behind erectile response [5], which has led to our current biological focus on the causes and treatment of ED.

Because an appreciation of the biological causes of ED emerged secondary to advances in physiological and biochemical research, as well as pharmacological advances, the dichotomous classification of the causes of ED as either biological/organic or psychological in nature has persisted [6] and has been maintained in the diagnostic systems until the 11th revision of the WHO International Classification of Diseases and Related Health Problems (ICD-11) [7]. This dichotomy is reductive and does not capture the complexity of the factors that influence the development and treatment of sexual dysfunctions such as ED. Although exquisite biological and/or psychological delineations of ED might be found, it has been argued that it is necessary to integrate an understanding of these factors more comprehensively in contemporary ED management [8]. Indeed, biological and psychological factors likely appear in combination in most people with a diagnosis of ED [9] and may both therefore be targeted. Within the dominant biological model of ED in modern medicine, there is a need to understand the influence of psychiatric, psychological and relational/social factors to enhance treatment and improve outcomes for affected men.

Importantly, evidence suggests that there is a notable link between psychological or psychiatric factors and ED. For instance, personality traits such as high neuroticism and low extraversion have been associated with ED in a meta-analysis of 137 studies exploring the link between personality traits and sexuality or sexual health [10]. This evidence likely reflects how personality traits might impact lifestyle factors, sexual attitudes and sexual schemata and even determine sexual dysfunction [9, 11]. For instance, high levels of neuroticism and low levels of extraversion has been linked to a greater likelihood of cigarette smoking and lower levels of physical activity, which are both linked to ED [12, 13]. Furthermore, ED has also been linked to self-defeating personality traits [11, 14]. Individuals with self-defeating personalities, indeed, tend to engage in self-critical thinking, which can elevate stress levels. Elevated stress and anxiety are well-established contributors to ED as they interfere with the brain's capacity to initiate and maintain physiological arousal. To this end, there is also a relationship between stress, as an acute or chronic psychological state, and ED [9]. In the acute situation, stress related to sexual performance (i.e. performance anxiety) can have negative effects on the potential for a successful erection [15]. Factors associated with cognitive processing have been found to play a significant contribution to sexual function among men, with the potential for chronic cognitive features to result in disengagement and a loss of sexual behaviours [9]. In additional, the psychological impact of chronic stress related to work has been linked to the potential for ED as a consequence of hormonal and neurological mechanisms [16].

There is evidence that psychiatric disorders such as generalised or reactive anxiety and depression are prevalent in men with ED [17–19]. This seems to be particularly pronounced in younger men, where anxiety and depression are considered the main risk factors for ED [8]. The severity of ED is also associated with both the prevalence and severity of anxiety and depression in young men [20–22]. However, caution is needed when attributing causation within this relationship as many

evaluations are cross-sectional in nature, and mechanisms could be presented to describe ED as causing anxiety or depression or vice versa. For instance, psychosocial distress may be associated with ED and may lead to the development of depression, while depression can be associated with a risk of sexual dysfunction, the loss of libido and ED [18]. Evidence supporting a causative relationship between ED and subsequent depression includes a 5-year follow-up study of 2527 men with ED that found that this group had a higher risk of developing depression compared with age- and sex-matched controls [23]. Conversely, studies in middle-aged and older men show a predictive role of depressive symptoms, or depression diagnosis, for future risk of ED [24]. Furthermore, a 27-year longitudinal study of 787 male twin veterans found that total depression symptoms were associated with a 32% increase risk of subsequent development of ED compared with men without depression symptoms at baseline [25].

A bidirectional relationship between depression and ED has been suggested in the literature. A 5-year follow-up study of 1683 men who completed questionnaires on depression and ED symptoms found that moderate or severe depression (or antidepressant use) increases the subsequent risk of ED, while ED was an independent risk factor for depression or the exacerbation of depressive symptoms [26]. Furthermore, a meta-analysis of 49 studies found that men with depression have a 39% increased risk of ED compared with men without depression, while the converse relationship was also true with ED linked to a nearly threefold increased risk of depression [18].

In patients with anxiety disorders, as well as post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, social phobia or social anxiety disorder, the prevalence of ED was reported to be around 20% [27]. This may also reflect a bidirectional relationship, with one study showing that both anxiety and depression showed a high incidence before and after the diagnosis of ED in young men (aged 18–40 years) compared with men without ED [28]. Therefore, healthcare professionals should be aware of the potential for anxiety and depression to both contribute to the risk of ED and occur as a consequence of ED.

Although conditions such as depression and anxiety are among the key factors contributing to ED, psychotic disorders, such as schizophrenia, are also significantly associated with an increased risk of ED due to a combination of psychological, neurobiological and treatment-related factors. In men with schizophrenia, the negative symptoms—such as social withdrawal, apathy and emotional blunting—can reduce libido and lead to sexual dysfunction [29–32]. Additionally, symptoms like paranoia may disrupt intimate relationships and diminish both motivation and opportunities for sexual activity, indirectly contributing to ED [33]. The neurobiology of psychotic disorders also plays a role; neurotransmitter dysregulation, particularly of dopamine, impacts pleasure and sexual arousal pathways, increasing vulnerability to ED [34]. Additionally, psychological symptoms that are associated with a biological cause may also have an impact on sexual dysfunction and the risk of ED.

Although psychiatric symptomatology plays a pivotal role in the onset of multiple sexual dysfunctions, among them ED, one must bear in mind how the weight of psychopharmacological treatment might affect sexual health and erectile function. Medications for depression and anxiety, particularly certain classes of antidepressants and anxiolytics, are known to contribute to the development or worsening of ED. Selective serotonin reuptake inhibitors (SSRIs), for instance, are widely prescribed for anxiety and depression but are also associated with sexual side effects, including reduced libido, delayed ejaculation and ED [35]. These side effects are attributed to an increase in serotonin levels, which can interfere with sexual arousal and the body's ability to maintain an erection and achieve orgasm. Notably, some individuals experience post-SSRI sexual dysfunction (PSSD), where sexual dysfunction symptoms, such as ED, persist even after discontinuing the medication, highlighting a complex and often long-lasting side-effect profile associated with SSRIs [36]. The prevalence of PSSD needs to be investigated in future studies.

Similarly, other classes of antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants and certain mood stabilisers, can negatively impact sexual function, although to varying degrees. Medications like SSRIs and SNRIs may impair erectile function by inhibiting nitric oxide synthesis, which is essential for penile blood flow and erection [37].

Anxiolytics, including benzodiazepines, can also cause or worsen ED by dampening central nervous system activity, which may reduce sexual desire and interfere with erectile function. Benzodiazepines and similar agents work on the GABAergic system, which, while effective for reducing anxiety, can negatively affect libido and arousal by decreasing neural responsiveness [38].

Antipsychotic medications are also associated with many sexual side effects, including high rates of ED [34]. Many antipsychotics block dopamine receptors, reducing dopamine levels crucial for sexual arousal. Some antipsychotics, particularly those such as risperidone and haloperidol, elevate prolactin levels, leading to hyperprolactinemia, which is strongly associated with sexual dysfunction, including ED [34].

Overall, this section has demonstrated that psychological, psychiatric and relational/social factors are closely linked to ED. This is an important association to consider in clinical practice, highlighting the importance of looking beyond the organic causes of ED and taking a holistic view of the patient. The relationship between psychological, psychiatric and relational/social factors and ED is conceptualised in Fig. 4.1. In this model, the role of these factors is considered alongside organic/biological risk factors for ED. Rather than being considered separate risk factors, psychological, psychiatric, relational/social and biological factors may have a variety of links and may be associated at a mechanistic level [9]. This is considered further in the next section, with an evaluation of the importance of stress and hormonal changes in influencing erectile function.

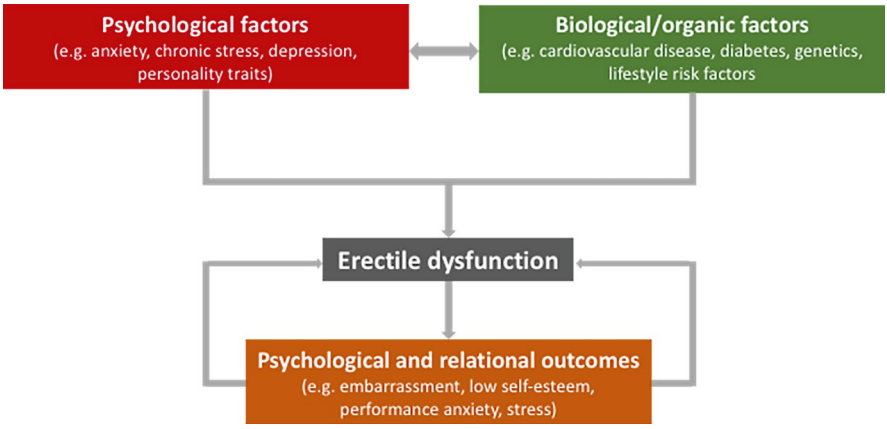


**Fig. 4.1** Model of key psychological contributors to erectile dysfunction. This figure illustrates the psychological factors linked to erectile dysfunction and their relationship with biological/organic risk factors [9, 39]

## 4.2 The Role of Stress-Induced Hormonal Changes and Their Effects on Erectile Function

One of the mechanisms linking psychological well-being to physical health is the impact of stress on physiological or biological function. Specifically, stress may have important effects on hormones, which can be particularly relevant in the context of erectile function [40]. The hormonal control of erectile function is well established, particularly regarding the role of testosterone in influencing sexual arousal/libido, autonomic nervous function and the stimulation of nitric oxide synthase in the endothelium of penile arteries [1]. Other hormones are also associated with specific effects on sexual function, including oxytocin, growth hormone, prolactin, thyroid hormones and hormones linked to metabolic control [41–43]. A contemporary synthesis of the role of the endocrine system in ED is presented in Chap. 6.

Importantly, hormone levels are influenced by psychological well-being, which may be illustrated by evaluating the link between cortisol (the stress hormone) and ED. It is established that chronic stress and mental health conditions are associated with elevated cortisol levels and increased sympathetic nervous system activity (relative to parasympathetic activity), potentially disrupting erectile function [16]. Elevated cortisol levels are also correlated with sleep disorders and depression, which has been linked with ED [44]. Stress has been linked to sympathetic activity and elevated cortisol levels, which may provide a basis for a reduction in sexual function under stress conditions [16]. For instance, cortisol levels showed negative correlations with domains of erectile function and sexual desire in one study [45]. Other data support a link between cortisol levels and impaired sexual function. For

instance, in patients with chronic diseases, exogenous corticosteroid administration at supraphysiological doses is linked to the development of ED [46]. Furthermore, it has been reported that 69% of men with endogenous hypercortisolism have a decreased libido [47, 48]. Another study reported a negative correlation between erectile function and perceived stress scores and between an increase in cortisol levels 45 minutes after waking and sexual desire scores in men with ED [49]. The negative effects of stress on libido and subsequent erectile function may therefore be mediated via cortisol levels [49].

Cortisol levels in the blood increase at the same time as noradrenaline when the sympathetic nervous system is dominant [50]. Sympathetic activation has been shown to restrain erections [16]. Parasympathetic activity may be more pronounced at the point of initiation of sexual arousal and erection, which can precipitate a drop in cortisol levels due to the down-regulation of the hypothalamic-pituitary-adrenal (HPA) axis activity [16]. Cortisol levels decline in the blood and the cavernous compartment with the initiation of penile erection [51]. Recent data also illustrate that cortisol may act as an antagonist of normal sexual response in adult men [52]. This study enrolled 54 healthy adult men and 45 men with ED and included serial blood sampling from the cubital vein and corpus cavernosum during different stages of the sexual arousal cycle to determine changes in cortisol levels. In men without ED, cortisol levels decreased in cavernous and systemic blood at the beginning of sexual stimulation, with a further decrease in cortisol during detumescence. In contrast, patients with ED had no significant changes in cortisol in systemic or cavernous blood samples throughout the sexual arousal cycle [52]. These findings support the potential for cortisol to antagonise erectile function, with dysregulation in cortisol secretion or degradation potentially playing a role in ED, although the mechanism of this association remains uncertain.

From a mechanistic perspective, high levels of cortisol or a failed cortisol drop at the point of sexual arousal may lead to ED as a consequence of the direct effects of cortisol in cavernous tissue [16]. Indeed, high cortisol levels impair the response to intra-cavernosal injection of smooth muscle relaxants through an unknown mechanism [53]. However, this observation may reflect a broader disruption of sympathetic/parasympathetic control and the regulation of the HPA axis, with cortisol levels serving as a marker of this disruption. A recent study including 75 men with ED and 75 healthy men found that there was a clear relationship between stress scores, higher parasympathetic activity and higher cortisol awakening responses in men with ED, with higher stress scores seen in men with ED [54]. Therefore, a complex relationship between stress, parasympathetic activity and cortisol levels may be linked to erectile function.

Stress-induced changes in other hormones beyond cortisol have been observed in the literature. For instance, data from animal models suggest that prenatal stress exposure in rats is associated with an increase in androgen thresholds related to penile reflex and sexual behaviour [55]. In humans, testosterone, a key androgen associated with erectile function, has been found to show differential responses in acute or chronic stress situations [56]. Testosterone levels may be increased during acute stress situations and decreased in the context of chronic stress [57]. This is

consistent with the view that in acute stress situations, the regulation of testicular function is governed by cytokines and fluctuations in circulating levels of gonadotropins, while in chronic stress, regulation reflects changes consistent with adaptations in the HPA axis, linked to hypogonadotropic hypogonadism [40]. Specifically, stress responses are regulated by the paraventricular nucleus in the hypothalamus, which can activate the sympathetic–adrenal system and the HPA axis, suppressing the hypothalamic-pituitary-gonadal (HPG) axis and testicular Leydig cells, reducing testosterone levels [40]. The link between androgens, such as testosterone, and the risk of ED has been broadly established. However, most data linking stress-induced changes in androgens to the potential for ED are based on animal models, and the precise influence of these changes on ED risk needs further clarification. Similarly, stress-induced changes in catecholamines and other hormones linked to sexual function warrant further exploration in this context. For instance, it has been shown that elevated prolactin levels are associated with psychosocial stress and ED [58], emphasising the close link between stress and a range of hormones that may be implicated in the development and maintenance of ED [59].

Overall, this chapter illustrates that stress, hormonal control and ED may be closely related, providing support for a mechanism where stress-induced hormonal changes may impact erectile function. Stress is an important marker of psychological well-being and may be influenced by a range of internal and external factors. These factors include biological, relational and psychological challenges, highlighting the complex nature of the regulation of erectile function. A summary of the mechanisms linking stress-induced hormone changes to ED is presented in Fig. 4.2. Regardless of the specific mechanism, stress and psychological well-being have

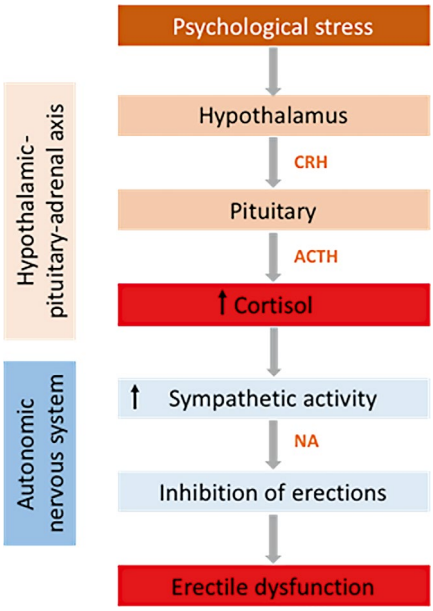


**Fig. 4.2** Stress-induced changes in hormone levels and the mechanisms linking these changes to erectile dysfunction. Abbreviations: *ACTH* adrenocorticotropic hormone; *CRH* corticotropin-releasing hormone, *NA* noradrenaline

been strongly associated with physical health outcomes, including the risk of cardiovascular events and non-communicable diseases [60]. The potential for ED to serve as an indicator of these physical health outcomes in people with poor psychological well-being is considered in the following section.

## 4.3 Correlation Between Psychological Well-Being and Physical Health Outcomes Using ED as an Indicator

The link between psychological, psychiatric and relational/social factors and the potential for stress-related hormonal changes that impact erectile function has relevance in understanding how these factors may be linked to the onset of ED. Poor psychological well-being may be a contributing factor to ED, but it is also an important consequence of the condition that is potentially damaging relationships, reducing self-esteem and causing stress and anxiety [9]. These psychological consequences of ED can reduce the potential for positive health outcomes [61].

Psychological stress may be a risk factor for poor physical health outcomes [62]. Psychological stress is specifically linked to a higher risk of mortality in patients with multimorbidity [63]. A meta-analysis of 15 studies indicated that individuals reporting high levels of psychological distress had a 28% higher risk of cardiovascular disease compared with those with low or no psychological distress [64]. Conversely, psychological well-being is associated with protective effects against mortality, with both all-cause and cardiac mortality linked to well-being [62]. In addition, psychological well-being has been associated with the onset and course/progression of chronic diseases and the risk of cardiovascular events [62].

The relationship between ED and psychological well-being is bidirectional, as noted at the beginning of this chapter when considering how anxiety and depression may be present prior to or following the onset of ED. There is a complex relationship between psychological stress, mental health and ED [65]. For instance, ED may cause poor psychological well-being by impacting interpersonal relationships, confidence, self-esteem and other variables [9]. It is also apparent that the treatment of ED reduces psychological distress in men [66], in addition to directly improving erectile function and additional health outcomes.

The presence of ED can be indicative of pre-existing psychological factors or may be related to future risk of these factors. Given that psychological well-being is linked to health outcomes, it may be considered that ED is an indicator of the potential for poor physical health in patients with compromised psychological well-being. There are specific instances where ED may provide insight into the associations between psychological and physical health. For instance, it has been observed that men with ED show a greater deterioration in both psychological well-being and physical health outcomes compared with men without ED [67]. In addition, ED is an independent risk factor for cardiovascular events [68]. It has also been demonstrated that psychological stress as a result of ED may increase cardiovascular risk [66], while depressive mood is also associated with an increased risk of adverse cardiovascular outcomes [69]. Furthermore, in men with type 2 diabetes mellitus,

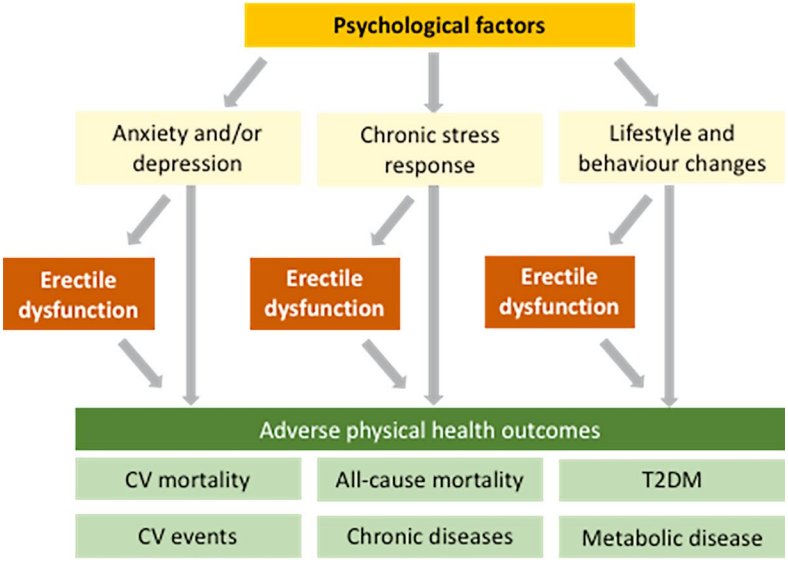


**Fig. 4.3** Conceptual diagram linking psychological well-being, erectile dysfunction and physical health outcomes. This figure illustrates how erectile dysfunction may emerge as a consequence of psychological factors, with the presence of erectile dysfunction serving as a marker for subsequent physical health problems

the presence of ED may be considered a risk factor for future complications and cardiovascular events [70]. This reflects not only the role of ED as an early cardiovascular risk marker but also the potential for ED to contribute to psychological stress and mental health conditions, which are in turn also linked to poor outcomes in populations with diabetes [71].

Therefore, ED may therefore be an indicator of the potential for poor physical health outcomes in patients with poor psychological well-being. A conceptual illustration of this link is presented in Fig. 4.3. The relevance of this for screening and treatment in men presenting with ED is considered in the following section.

## 4.4 Importance of Psychological Screening and Interventions for Men Presenting with ED

Data suggest that psychological problems are common among men with ED and may have a negative impact on wider well-being and health outcomes, as well as erectile function [20, 72]. The bidirectional nature of the link between psychological factors and ED, as well as the strong associations noted in the literature, suggests that there is a need to consider the evaluation of psychological well-being among men presenting with ED. Psychological well-being is a determinant of future health outcomes, and thus earlier identification and management of psychological disorders can facilitate improvement in those outcomes [73]. In addition, psychological

symptoms and mental health conditions may influence well-being, adherence and treatment outcomes for ED, reinforcing the need for psychological screening in men with ED [74].

The effects of ED on psychological outcomes are potentially diverse in nature and warrant a thorough approach to screening and evaluation. Recent European guidelines on the diagnosis and management of ED [8] recommend that educational, psychological, psychosexual and marital assessment is completed in all men presenting with ED, regardless of whether psychological factors are considered important in the aetiology of their ED. Limiting such assessments to patients who lack clear biological causes for ED is not recommended as this perpetuates the dichotomous thinking of organic versus non-organic ED while overlooking the potential for ED to generate intra-psychic or relational challenges [8]. Key features of a robust assessment should include an evaluation of psychological symptoms or risk factors, as well as consideration of cognitive, emotional and relational aspects linked to ED. This may require multidisciplinary input as medical professionals may lack the knowledge and skills to perform robust psychological evaluations in this context [8]. The inclusion of the sexual partner of the patient within these discussions can be of value, particularly in providing additional details on the circumstances in which ED occurs and also in supporting the patient during management [21].

Psychiatric evaluations are also recommended in the recent guidelines [8] and include the use of self-reported scales to determine anxiety and depression symptoms. For instance, the General Anxiety Disorder-7 (GAD-7) scale has value in identifying patients with anxiety, while the Personal Health Questionnaire-9 (PHQ-9) provides a swift screening tool for depression symptoms [19]. Both of these tools have been shown to have value in detecting anxiety and depression symptoms in men with ED [75, 76] and can provide a reliable screening process to guide the referral and/or treatment of patients with anxiety or depression [8].

Once an evaluation has been performed, there is a need to initiate appropriate interventions and education to target identified causes or sustaining factors for ED. Interventions for psychological conditions can have a positive impact on a range of outcomes related to ED, including sexual function, stress and anxiety levels, relationship quality and communication within the relationship [21]. These findings are also evident when psychological therapies are combined with other treatment modalities, such as PDE5is [77, 78]. ED treatment approaches may include psychosexual counselling or other interventions aligned with the identified needs, goals and expectations of the patient in relation to sexual function outcomes [21]. For instance, cognitive behavioural therapy (CBT) and other sex therapies may have value in improving sexual outcomes in patients and couples (summarised in Table 4.1), while the use of mindfulness-based interventions may also be considered in this patient group, with growing evidence of the inverse relationship between mindfulness and sexual dysfunction, including ED [79].

The value of psychological interventions in patients with ED is highly dependent on overcoming barriers to treatment [21]. For instance, men may experience embarrassment, low self-confidence and communication problems with partners, which may interfere with help seeking and may influence attitudes towards treatments [9].

**Table 4.1** Summary of the characteristics of studies evaluating psychological interventions in men presenting with erectile dysfunction

| Author and date | Design | Participants | Interventions | Erectile function outcome |
|---|---|---|---|---|
| Khan et al. [80] | Quasi-experimental | 60 men | CBT + PDE5i vs PDE5i alone | IIEF |
| Khan et al. [81] | Follow-up (18 months) | 20 men | CBT + PDE5i vs PDE5i alone | IIEF |
| Bilal et al. [82] | Feasibility study, randomised | 28 men | CBST vs sildenafil | IIEF-5 |
| Abdo et al. [83] | RCT | 110 men | Group counselling therapy vs sildenafil vs combined therapy | MSQ, SHIM |
| Melnik et al. [84] | RCT | 22 men | Group psychotherapy vs sildenafil vs combined therapy | EDITS |
| Aubin et al. [85] | Pilot RCT | 44 couples | Sildenafil +/− couple sex therapy | IIEF |
| Boddi et al. [86] | Pilot RCT | 30 couples | Vardenafil +/− CBST | IIEF |

Abbreviations: *CBST* cognitive behavioural sex therapy, *CBT* cognitive behavioural therapy, *IIEF* international index of erectile function, *MSQ* male sexual quotient, *RCT* randomised controlled trial, *SHIM* sexual health inventory for men

Furthermore, unrealistic expectations, stigmatisation and healthcare professional communication styles can influence treatment acceptance [21]. Therefore, the healthcare professional should be aware of these barriers and should adopt appropriate communication styles and share decision-making approaches to ensure that treatment is feasible and acceptable [21].

## 4.5 Implications of ED as a Pre-emptive Sign of Potential Mental Health Concerns

It has been recognised that the appearance of ED may be an important early marker of poor physical health, including cardiovascular disease risk [87]. This reflects the vulnerability of the mechanism of normal erectile function to a range of stressors and pathological effects and may be evolutionarily tied to the fitness of males [88]. Hence, the presence of ED can be an indicator of future health risk, particularly with respect to cardiovascular and metabolic conditions. However, fitness is not only determined by these physical health markers, and the potential for ED to serve as a marker of psychological fitness may be equally important.

Given the association between ED and psychological factors, including mental health disorders, there may be value in considering ED as a risk factor for future poor mental health. Research suggests that ED has links with psychological stress and may be more likely in people with chronic stress or specific personality traits, while ED itself can result in increased stress, anxiety and other negative psychological outcomes, increasing the risk of mental health problems [27]. Therefore, in men

with ED, consideration of psychological well-being is important, and an evaluation of psychological well-being and mental health outcomes should be performed during treatment [65, 89].

In conclusion, the following points can be considered important when evaluating ED in the context of mental health:

- The presence of ED is a marker of risk factors and poor health outcomes in affected men.
- The identification of ED should prompt an early assessment of physical and psychological conditions in the patient.
- Mental health problems may emerge in ED as a consequence of pre-existing risk factors.
- Poor mental health may also occur secondary to the stressors linked to ED or to physical conditions seen in patients with ED (e.g. type 2 diabetes and cardiovascular disease).
- While not all patients with ED will experience mental health problems, the presence of ED is a potential pre-emptive sign of mental health concerns and poor psychological well-being.

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# 5 Lifestyle Interventions to Pre-empt Erectile Dysfunction and Associated Comorbidities

Andrea Sansone and Ege Can Serefoglu

**Abstract**

Lifestyle factors have an important influence on the risk of cardiovascular disease and wider non-communicable diseases. The potential for erectile dysfunction (ED) to serve as a sensitive indicator for these conditions highlights how lifestyle risk factors can influence ED risk directly. This chapter explores the link between lifestyle risk factors and the development of ED, highlighting the interrelated nature of these risk factors in pathogenic mechanisms. The potential for lifestyle interventions to modify the risk of ED and to treat this condition is evaluated with respect to published evidence on this topic and the public health implications of such approaches. The potential to modify not only the risk of ED but also the associated conditions for which ED may be a precursor illustrates the importance of effective lifestyle risk factor management in men.

**Keywords**

Lifestyle · Erectile dysfunction · Comorbidities · Obesity · Physical activity · Smoking

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## 5.1 Lifestyle Factors That Contribute to Erectile Dysfunction

It is well known that lifestyle risk factors contribute to cardiovascular disease, as well as other non-communicable diseases. Previous chapters have highlighted the role of erectile dysfunction (ED) as a sensitive indicator of the negative effects of risk factors that contribute to non-communicable diseases. The extent to which ED may be an early marker of these conditions is supported by the artery size hypothesis, where small-diameter blood vessels in the penis are more susceptible to disease than larger-diameter arteries, such as in the coronary vasculature [1–3]. Therefore, an understanding of how these risk factors may contribute to ED directly is an important topic, with the potential to reveal opportunities for lifestyle interventions and preventative strategies against ED and for the wider lifestyle-related conditions for which ED may be an early indicator.

Lifestyle risk factors (summarized in Fig. 5.1) comprise a diverse range of parameters that can contribute towards the potential for poor health, as well as poor sexual health [4]. There is a particular emphasis on the importance of cardiovascular or cardiometabolic risk factors and the incidence of ED in the published literature [5]. These risk factors include some non-modifiable factors, such as age, which are associated with the onset of ED. However, modifiable risk factors also appear to have a strong association with ED [6]. These risk factors may account for observed

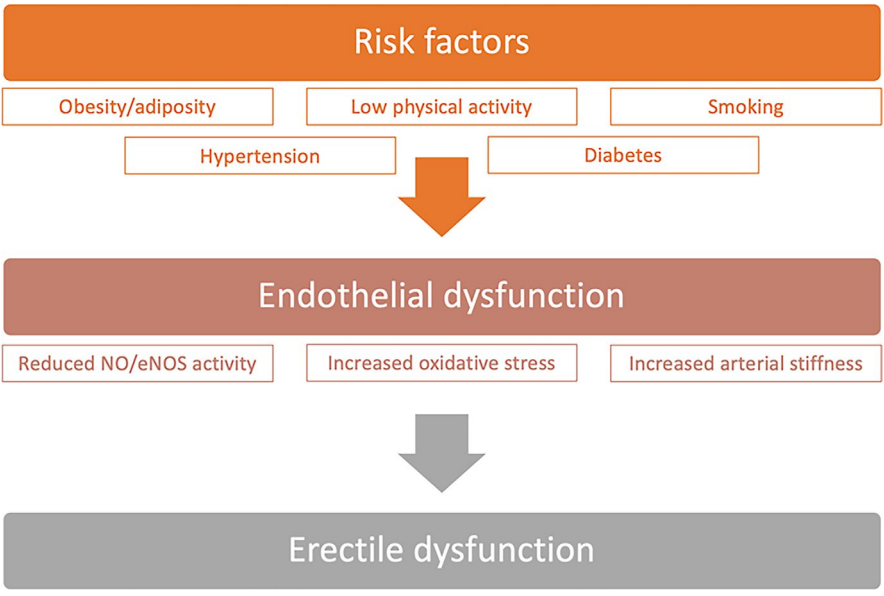


**Fig. 5.1** Diagram showing how risk factors contribute to ED. This diagram demonstrates the link between lifestyle/modifiable risk factors and the key pathogenic pathways of ED, including endothelial damage and dysfunction. Additional mechanisms are highlighted, along with non-modifiable risk factors that add complexity to the prevention of ED. Abbreviations: *eNOS* endothelial nitric oxide synthase, *NO* nitric oxide [56]

**Table 5.1** Summary of the key lifestyle risk factors for erectile dysfunction (ED)

| Lifestyle risk factor | Mechanism of action and contribution to ED |
|---|---|
| Obesity or weight gain | Oxidative stress [7]<br>Endothelial dysfunction [8]<br>Systemic inflammation [9]<br>Hypogonadism [10]<br>Body image dissatisfaction [11]<br>Leptin and insulin resistance [12, 13] |
| Low physical activity levels | Contribution to weight gain [14] and associated inflammation, endothelial dysfunction, oxidative stress and leptin and insulin resistance [15, 16]<br>Wider effects on blood pressure and cardiovascular health [17–19] |
| Smoking | Endothelial damage [20]<br>Impaired nitric-oxide-synthase-mediated vasodilation [21–23]<br>Arterial stiffness [24]<br>Increased rho-associated kinase activity [25] |
| Hypertension | Smooth muscle hypertrophy and impaired endothelial function [26] |
| Diabetes | Complex interplay of vasculopathy, neuropathy and nephropathy [27] |
| Hypercholesterolaemia | Oxidative stress and impaired endothelial function [28] |

Common lifestyle risk factors for ED are noted based on those with the greatest support in epidemiological studies, including their mechanism of action in relation to ED onset.

effects, such as the link between ED and older age, as the accumulation of modifiable risk factors and comorbidities with advancing age may be of greater significance than age itself in determining ED risk [6]. The following sections consider the key modifiable lifestyle risk factors that have been associated with ED, focusing on their significance, potential mechanism of action and inter-relationships (summarised in Table 5.1).

### 5.1.1 Obesity

Increasing body mass index (BMI) or a state of obesity (BMI $\geq$ 30 kg/m$^2$) has been associated with ED [29–32]. Data from the Health Professionals Follow-up Study, the National Health and Nutrition Examination Study and the Massachusetts Male Ageing Study all agree that there is a 1.5- to threefold increased risk of ED in men with a BMI $\geq$ 25 kg/m$^2$ compared with those with a BMI < 25 kg/m$^2$, with risk further increasing in those with obesity [33–35]. Other studies support an association between high BMI and ED. Walczak et al. found that of men with ED symptoms lasting for at least 6 months ($n$ = 154), 79% had a BMI > 26 kg/m$^2$ [36], while a recent study by Liu et al. found that 70% of men with ED were obese compared with 34% in men without ED in an analysis of 878 men attending an andrology clinic [16]. In addition to BMI, other markers of adiposity are also correlated with ED risk. For instance, in a Slovakian study of 216 men, 74.7% of those with abdominal obesity (waist circumference > 94 cm) had some degree of ED, with an association between increasing waist circumference and ED incidence [37].

The mechanism through which obesity or increased BMI leads to ED is thought to be multifactorial, reflecting the role of obesity as a contributor to metabolic syndrome and cardiovascular disease. This includes effects related to oxidative stress and endothelial dysfunction, systemic inflammation and leptin and insulin resistance [16]. For instance, oxidative stress associated with obesity is linked to the attenuation of the endothelial relaxation of the corpus cavernosum and an increase in cytokines that suppress endothelial nitric oxide synthase, reducing erectile function [38]. Low-grade systemic inflammation seen in obesity is linked to elevated systemic inflammatory markers and cytokines that impair endothelial function [39]. Leptin resistance is linked to the suppression of testosterone levels, which can adversely affect erectile function [40], while insulin resistance is associated with increased systemic inflammatory markers, impaired vasodilation and severity of ED [41, 42]. Fat accumulation might lead to a hypogonadal state through other mechanisms, such as cytokine-induced suppression of the gonadal axis [43]. These effects may form a continuum of greater risk of ED with increased weight from normal levels, as well as increases in adiposity through other anthropometric values (e.g. waist circumference) [44].

### 5.1.2 Physical Activity Levels

Physical activity levels have been associated with ED in published literature [29, 30, 32]. It was reported that 45.8% of men with ED did not regularly engage in physical activity compared with 31.1% of men without a history of ED [29]. In men aged 40–75 years, engagement in physical activity has been demonstrated as an independent factor inversely related to ED [45], while data from men with type 2 diabetes showed that sedentary time demonstrates a significant positive association with ED risk [46]. Data from over 4000 men in the US National Health And Nutrition Examination Survey 2001–2004 found that participation in specific types of physical activity, such as leisure activities and vigorous physical activity, is linked to a lower risk of ED [47]. Together, these data suggest that physical activity levels may be generally protective against ED, while higher levels of sedentary behaviour are associated with ED, although the limitations of cross-sectional data sets should not be overlooked when considering causative effects.

The mechanisms through which physical activity levels influence ED risk relate to the effects of physical activity on weight, as well as wider metabolic risk linked to sedentary behaviours [47]. Physical activity that results in weight loss may be associated with reductions in inflammation, insulin and leptin resistance and oxidative stress [13]. Furthermore, physical activity may be associated with metabolic benefits independent of the effects on weight loss, such as a reduction in endothelial cell apoptosis and improvement in endothelial function [48]. Physical activity may also have positive effects on wider cardiovascular health, blood pressure and glycaemic control, as well as play a role in reducing oxidative stress and inflammation, all of which have been implicated in the development of ED [17–19].

### 5.1.3 Smoking Status

Smoking status has been linked to the risk of ED, with a higher incidence of ED noted in former or current smokers (19.1% and 21.1%, respectively) compared to never smokers in a cross-sectional analysis of over 2000 adult men from the USA [29]. Men with ED were more likely to have a history of current smoking than those without ED in the same study (27.2% versus 21.3%, respectively) [29]. A cohort of 513 middle-aged men from the Massachusetts Male Aging Study, excluding those with baseline diabetes or cardiac disease and poor erectile function, showed a risk ratio of 1.97 (95% confidence interval of 1.07–3.63) for developing ED when adjusting for age and hypertensive medication use [49]. Data from a cohort of 1130 men aged 50–70 years in Finland similarly found an increased risk of ED linked to smoking behaviour over a 10-year follow-up period, with an odds ratio of 1.4 (95% confidence interval of 0.9–2.2) [50]. A systematic review of eight case-controlled and cohort studies ($n$ = 28,586 men) showed a pooled odds ratio of 1.81 (95% confidence interval 1.34–2.44) for active smokers developing ED [51]. Therefore, data strongly supports a link between smoking and the risk of ED [52].

The negative effects of smoking on erectile function have been linked to the observed decrease in endothelial nitric oxide synthase activity seen in in vitro and in vivo models [53]. Cigarette smoking is associated with the potential to damage the vascular endothelium and impair nitric-oxide-synthase-mediated vasodilation, leading to ED [20]. The effects of smoking may also include changes to the elasticity of blood vessels, leading to arterial stiffness [24], as well as increases in Rho-associated kinase activity, which plays a role in maintaining flaccidity by regulating smooth muscle sensitivity to calcium [25].

### 5.1.4 Other Risk Factors

Other modifiable risk factors have also been linked to ED, including hypercholesterolaemia, excessive alcohol consumption and poorly controlled diabetes [29, 30, 54]. These risk factors play an important role in facilitating cardiovascular disease through a variety of mechanisms, and therefore their link to ED pathophysiology is not surprising. Psychological factors may also be important in the development or maintenance of ED, including anxiety, depression and stress. Problematic pornography use and Internet abuse may also be associated with ED [55], although the degree to which the lifestyle modification of these factors may be of benefit is not well established.

### 5.1.5 Inter-Relationships Between Modifiable Risk Factors

Risk factors associated with the development and persistence of ED may have specific mechanisms linking them to cardiometabolic outcomes, but they often coexist in the same individual and reflect a complex, interconnected set of factors that

influence health [56]. For instance, physical activity status and obesity may be independent predictors of ED but are closely linked in practice populations. There is a notable prevalence of comorbid conditions and disease states, including hypertension and diabetes, in people with ED that may be accounted for by the action of multiple risk factors [16]. Indeed, sexual health reflects a complex interplay of multiple factors, including cultural, intra-psychic, medical, relational and social aspects, and it can be expected that risk factors for ED would therefore be numerous and interconnected across these domains [56]. A systems medicine approach to understanding risk factors for ED recognises the importance of lifestyle risk factors that relate to cardiovascular risk and disease (e.g. smoking, obesity, physical activity levels, etc.) and how these are related to each other and other risk factors, spanning endocrine, immunologic, neurologic and urologic domains, among others [56]. Addressing these risk factors therefore requires a comprehensive approach aligned with systems medicine, including lifestyle modifications that may target one or more risk factors simultaneously. It is also worth considering that, in many cases, clinically relevant ED might be preceded by a "subclinical" form (subclinical ED (SED)) that might affect the individual's and the couple's sexual function despite failing to meet the diagnostic criteria for ED [57]. Likewise, the severity of ED could be affected by other coexisting sexual dysfunctions [58–60], including subclinical premature ejaculation [61], or by other concomitant psycho-sexological derangements, including infertility [62], depression [63–65] or anxiety [66, 67].

## 5.2 Effectiveness of Lifestyle Modifications in Preventing and Treating ED and Implications for Broader Health

The identification of modifiable lifestyle risk factors for ED and wider cardiometabolic disease is crucial in providing a basis for targeted interventions [68]. It is advocated that lifestyle risk factor assessment is completed in men with ED and those at risk for ED to guide opportunities for prevention and management [69]. This section considers key lifestyle factors associated with ED and the opportunities for targeting these factors in the prevention and treatment of ED, as well as in the context of broader health outcomes (Table 5.2).

Obesity is a common lifestyle risk factor associated with ED and is typically targeted through physical activity interventions or dietary interventions, which seek to redress the imbalance in energy consumption and energy expenditure driving weight gain [70]. Strategies intended to improve diet or increase physical activity may be used to facilitate weight loss in people who are overweight or obese [71]. Furthermore, physical activity interventions may have a preventative role in reducing the risk of weight gain while also conferring metabolic benefits in those without obesity, suggesting that exercise may have specific effects beyond weight control that can influence ED onset [15]. Studies have suggested that weight loss in men who are overweight or obese can lead to positive outcomes for erectile function (Table 5.2). A meta-analysis of randomised controlled trials focusing on weight loss strategies in overweight or obese men with ED showed a significant improvement in

**Table 5.2** Summary of randomised controlled trials evaluating the effectiveness of lifestyle modifications for treating erectile dysfunction

| Author and date | Country | Sample size | Features of intervention vs control | Outcome measures | Effect on erectile function |
|---|---|---|---|---|---|
| Maio et al. [84] | Italy | 60 | Aerobic exercise, moderate intensity, ≥ 3 hours per week + PDE5i therapy vs PDE5i alone | IIEF | At 3 months, IIEF restoration of erectile function was reported in 77.8% with intervention and 39.3% with control ($P < 0.004$) |
| Reis et al. [85] | Brazil | 20 | Lifestyle modifications for 4 months + gastric bypass surgery vs weekly follow-up | IIEF-5 | At 2 years, IIEF-5 score increased significantly with intervention vs control ($P = 0.0469$) |
| Wing et al. [86] | United States | 306 | Intensive lifestyle interventions for weight reduction and physical activity increases vs diabetes support and education | IIEF | At 1 year, intervention led to the worsening of erectile function in 8% and improvement in 22% vs 20% worsening and 23% improvement with control ($P = 0.006$) |
| Collins et al. [87] | Australia | 145 | Self-help, diet and exercise with online support vs waiting list control | IIEF-5 | At 6 months, significant improvement was seen in erectile function with intervention vs control ($P = 0.018$) |
| Khoo et al. [88] | Singapore | 90 | Calorie-controlled diet + low-volume moderate-intensity exercise (<150 minutes/week) vs calorie-controlled diet + high-volume moderate-intensity exercise (200–300 min per week) | IIEF-5 | At 6 months, the relative improvement in IIEF-5 scores was 14% with high-volume exercise and 10% with low-volume exercise ($P < 0.05$) |
| Maresca et al. [89] | Italy | 20 | Aerobic, moderate intensity exercise 3 × 40 min per week + PDE5i vs PDE5i and exercise advice | IIEF | At 2 months, IIEF-5 scores improved by 86% with intervention vs 27% with control ($P < 0.05$) |
| Jones et al. [90] | United States | 50 | Supervised walking 5 × 30–45 min per wk. at 55–100% $VO_2$ peak vs usual activity | IIEF | At 6 months, the prevalence of ED (IIEF <21) was reduced by 20% in the intervention group and 24% in the usual care group ($P = 0.406$) |

(continued)

**Table 5.2** (continued)

| Author and date | Country | Sample size | Features of intervention vs control | Outcome measures | Effect on erectile function |
|---|---|---|---|---|---|
| Begot et al. [91] | Portugal | 86 | Aerobic, mild-to-moderate intensity exercise (home-based walking), 4 × 30–50 min per week vs usual care and exercise advice | IIEF | At 1 month, the intervention led to improvement in ED in 71% vs the worsening of ED in the control group ($P < 0.001$) |
| Palm et al. [92] | Denmark | 154 | 12 weeks of physical exercise training (3 × 30 min interval cycling per week) + pelvic floor exercises + psychoeducation vs usual care | IIEF | At 4 months, erectile function improved in the exercise group compared with the control group (IIEF mean difference 6.7, $P < 0.0003$), which persisted to 6 months of follow-up |

Abbreviations: *ED* erectile dysfunction, *IIEF* international index of erectile function, *IIEF-5* 5-item international index of erectile function, *PDE5i* phosphodiesterase 5 inhibitor, $VO_2$ maximal oxygen consumption

weight loss and an improvement in erectile function compared with controls ($P < 0.01$ for both outcomes) [70]. Similarly, a systematic review of ten trials in men with ED showed that various levels of physical activity can contribute to improved erectile function over time [15]. An umbrella review of meta-analyses found that behavioural interventions, including targeted weight loss, produced significant effect sizes in managing ED, comparable to those seen with medication use, though with a greater level of imprecision [71].

The mechanisms of action of weight loss interventions may include the reversal of ED by decreasing inflammation, improving mood/self-esteem and increasing serum testosterone levels [54]. Importantly, positive effects can be seen in patients who show improved dietary habits without demonstrating clinically significant weight gain, reflecting improvements in other dietary influences on molecular pathways that can influence erectile function [72, 73].

Smoking cessation has a well-documented positive impact on cardiovascular health as it is linked to significant reductions in cardiovascular morbidity and mortality [74]. Prospective studies indicate that quitting smoking leads to measurable improvements in erectile function, with benefits observed as early as 1 year following cessation [75]. Smoking cessation strategies encompass a diverse range of behavioural and pharmacological interventions that support a reduction in smoking behaviours and an ultimate aim of stopping smoking altogether [76]. Where smoking cessation is not achieved, strategies that promote harm reduction in relation to smoking behaviours, such as the use of e-cigarettes and heat-not-burn devices, may be beneficial for overall health and for erectile function specifically [77, 78]. Indeed, a dose-dependent relationship has been noted between cigarette smoking and

erectile function, advocating for the promotion of strategies that reduce harm across all smokers, regardless of baseline smoking habits [79].

Other intervention strategies that may be considered to reduce ED prevalence and to improve erectile function in those with ED include alcohol reduction strategies, optimisation of hypertension management, improved diabetes control and other interventions targeted at the individual level [80, 81]. However, there is a need for robust clinical trial evidence on the effectiveness of interventions targeting these risk factors for reducing symptoms of ED. As many of these risk factors are linked to other health outcomes (e.g. cardiovascular risk), targeting them can impact the associated conditions in addition to ED and reduce negative health outcomes [82, 83]. Therefore, targeting cardiovascular risk factors in men with ED should be considered standard practice and aligned with wider strategies for health improvement.

## 5.3 Potential of Lifestyle Interventions to Prevent ED and Related Conditions

The importance of identifying lifestyle risk factors in men with ED, or at risk of ED, is that these factors present opportunities for lifestyle modification and the prevention or management of ED and associated comorbidities [93]. The majority of identified risk factors for ED are modifiable, and evidence-based interventions are widely available to target these factors. Targeting lifestyle risk can not only prevent and treat ED but also play a wider role in reducing cardiovascular and chronic disease risk [69, 93].

Despite the potential for lifestyle interventions in preventing and treating ED, there are some important challenges when targeting these risk factors in practice. For instance, non-modifiable risk factors, such as age, gender, ethnicity and family history are not amenable to direct interventions, although their identification may guide risk stratification and prompt earlier interventions for modifiable risk factors [93]. In addition, the opportunities to implement preventive measures may be limited in patients with lifestyle-based risk factors as this group may have no or infrequent contact with healthcare professionals until medical symptoms emerge or conditions are diagnosed [94, 95]. Once lifestyle factors have been identified, additional challenges exist in ensuring the effectiveness of interventions. Many lifestyle modifications rely on patient motivation and adherence to changes in the long term [82]. In addition, where medications are used to manage risk factors or symptoms, it is important to recognise the risks associated with counterfeit drugs, where adulteration with other drugs and unreliable dosing may be evident [96]. Healthcare professionals should play a role in educating patients and supporting appropriate prescribing practices to help mitigate risks. In addition, the role of the patient's partner in supporting adherence and facilitating the earlier identification of ED should not be underestimated [97, 98]. Consideration of these challenges to effective lifestyle modification in people with ED, or at risk of ED, is crucial when designing population health strategies targeting ED.

## 5.4 Population Health Strategies to Reduce the Incidence of ED Through Lifestyle Change

As noted previously, data from randomized controlled trials with a small or moderate sample size support the potential for multimodal lifestyle and weight loss interventions to improve ED in men who have cardiovascular risk factors, metabolic syndrome or type 2 diabetes mellitus (T2DM). Outside of the clinical trial setting, real-world evidence provides additional insights about how specific health strategies related to lifestyle factors may have an impact on ED.

The association between adherence to healthy diets and the incidence of ED in men without diabetes was examined in the Health Professional Follow-up Study, a large, population-based prospective cohort study of 21,469 male health professionals in the USA [99]. All participants were aged between 40 and 75 years at enrolment, with follow-up completed from 1998 to 2014. Food frequency questionnaires were used to evaluate nutrient and food intake every 4 years, with diet quality assessed using the Mediterranean Diet score and the Alternative Healthy Eating Index 2010 score. At a mean follow-up of 10.8 years, the study found 968 incident cases of ED in men younger than 60 years, 3703 cases in men aged 60–69 years and 4793 cases in men aged 70 years or older. The lowest risk of incident ED was seen in men younger than 60 years and with the highest category of Mediterranean Diet score compared with those in the lowest category (hazard ratio 0.78, 95% confidence interval 0.66–0.92). In older men, Mediterranean Diet score was inversely associated with incident ED, while high scores on the Alternative Healthy Eating Index 2010 showed a lower risk of incident ED, particularly in younger age groups. Together, the findings suggest that men who adhere to healthy diets have a lower risk of ED, supporting the role of diet in maintaining erectile function. The potential for population-targeted lifestyle and health strategies to reduce the incidence of ED needs to be explored further in other populations, but the findings of this study suggest potential value in this approach [99].

Further insights into the role of specific interventions that may be employed on a population level are noted in Table 5.3. These findings highlight how dietary factors may be targeted in high-risk patients for ED, including those with obesity and/or T2DM, where Mediterranean or low-calorie diets can have a positive impact on erectile function scores compared with other diets [100, 101]. In addition, the use of specific strategies in men with T2DM, including lifestyle interventions, intensive glycaemic control and phosphodiesterase type 5 inhibitor therapy, may be of greater benefit for preserving erectile function than lifestyle modifications and glycaemic control alone [102]. It is important to consider the target population and specific patient risk factors when applying trial data to real-world settings, allowing for targeted management approaches to ED prevention and symptom mitigation.

**Table 5.3** Summary of key population health strategies and their effectiveness in targeting erectile-dysfunction-related lifestyle risk factors

| Author and date | Population targeted | Intervention | Outcomes | Findings |
|---|---|---|---|---|
| Khoo et al. [101] | Men with ED and obesity from Asia ($n = 48$) | Meal replacement plan to reduce calorie intake by 400 kcal compared with a conventional reduced fat diet for 12 weeks | Weight, waist circumference, calorie and fat intake, IIEF-5, sexual desire inventory score, quality of life, plasma testosterone and endothelial function | Meal replacement plans led to a greater reduction in weight, obesity, calorie and fat intake compared with a conventional reduced fat diet; erectile function improved in both groups, along with endothelial function, plasma testosterone levels, quality of life and sexual desire scores |
| Kirilmaz et al. [102] | Men with ED due to T2DM ($n = 84$) | Lifestyle modifications (diet and exercise) and medical treatment for intensive glycaemic control with or without PDE5i therapy (2–3 weeks) | Changes in ED (IIEF-5) | 44.2% of patients showed an increase in IIEF-5 scores when managed with lifestyle interventions and medications for glycaemic control, compared with an increase in 55.8% of patients managed with this regimen, plus PDE5i therapy ($P = 0.012$) |
| Maiorino et al. [100] | 106 men and 109 women with newly diagnosed T2DM | Mediterranean diet vs low-fat diet | IIEF | Over 8.1 years of follow-up, men in the Mediterranean diet group had a lesser decrease in IIEF scores compared with those in the low-fat diet group ($P = 0.024$) |

Abbreviations: *ED* erectile dysfunction, *IIEF* 5-item international index of erectile function, *PDE5i* phosphodiesterase 5 inhibitor, *T2DM* type 2 diabetes mellitus

## 5.5 Public Health Policies That Consider ED Prevention as a Gateway to Improved Men's Health Outcomes

Public health policies have the potential to play an important role in improving men's health [103]. Targeting public health policy, and specific strategies, toward the prevention of ED can be considered an important method that has implications not only for men's sexual health but also for overall health. Health professionals play a key role in driving public health policies and in their implementation [103]. However, sexual medicine has been overlooked in the medical education curriculum in universities, and clinician knowledge on the importance of targeting ED using

**Table 5.4** Key recommendations for public health policies targeting ED prevention

| Key recommendations for public health interventions targeting erectile dysfunction |
|---|
| Erectile dysfunction should be a prompt for lifestyle risk factor assessment and management across care settings and professionals |
| Adequate management of erectile dysfunction should focus on both clinically overt and subclinical forms |
| Evidence-based strategies to target obesity, physical activity levels, dietary quality and smoking behaviours should be implemented |
| Relational factors, including other sexual dysfunctions and infertility, should be considered and managed appropriately |
| Patient adherence should be optimised using individualised strategies and behavioural approaches |
| Wider comorbidities should be assessed and their management optimised to reduce the risk of erectile dysfunction and other health outcomes |
| Ensure that socio-economic and sociocultural factors are considered to promote health equity |

lifestyle interventions may be inadequate as a result. Accordingly, there is a need for sexual medicine to feature more heavily in medical education contexts [104]. Improved training in relation to sexual medicine has the potential to improve the recognition of ED as an early indicator of cardiovascular disease and adverse outcomes, as well as being linked to poor physical and mental health [105].

Importantly, once clinicians are equipped with the knowledge and skills to facilitate the early diagnosis of ED, the management of this condition should include not only targeted symptomatic interventions but also lifestyle modifications. These should include a focus on individual patient risk factors, such as obesity, smoking and physical activity levels, as well as encompass wider management of comorbidities [93]. Data on lifestyle modifications suggest positive effects on ED and cardiovascular risk [54, 68, 82]. However, care is needed to prioritise strategies that are supported by the evidence base and can facilitate clinically meaningful improvements in outcomes while ensuring that patients are motivated and engaged in lifestyle change. In addition, wider structural barriers that may lead to health disparities should be considered in this context [103]. Public health policies are needed to target all relevant lifestyle factors and socio-economic/sociocultural factors, reduce health inequity, promote access to care, raise awareness and ensure the coordination of preventative measures and services (Table 5.4) [103, 106].

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# Erectile Dysfunction as a Clinical Indicator of Endocrine Disorders

6

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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

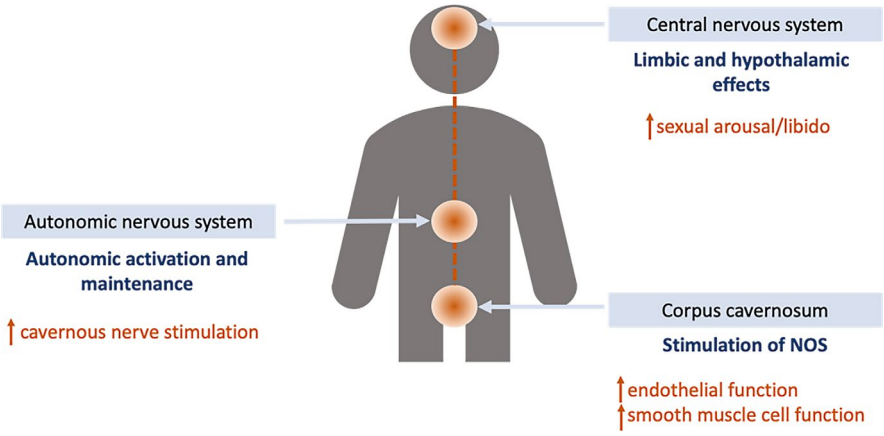


**Fig. 6.1** Testosterone actions in the control of sexual response and erectile function. This figure illustrates key targets of androgen/testosterone activity in the central nervous system, the autonomic nervous system and the corpus cavernosum, leading to erection. Abbreviation: *NOS* nitric oxide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

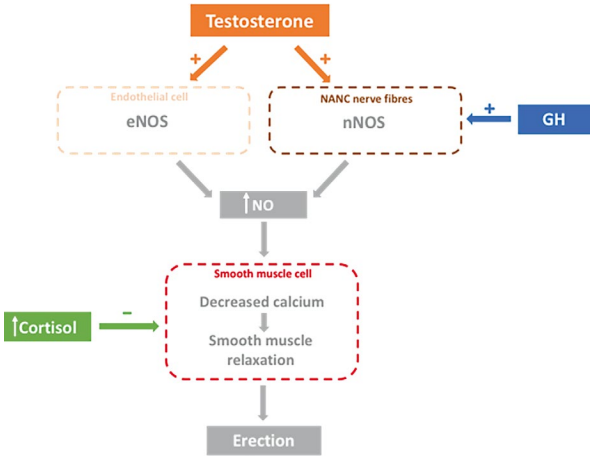


**Fig. 6.2** Interrelationship between endocrine axes and erectile function. In smooth muscle cells, nitric oxide (NO) triggers a decrease in calcium levels, mediated by cyclic guanosine monophosphate (cGMP), which causes smooth muscle cell relaxation and subsequently leads to penile erection. Testosterone 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;

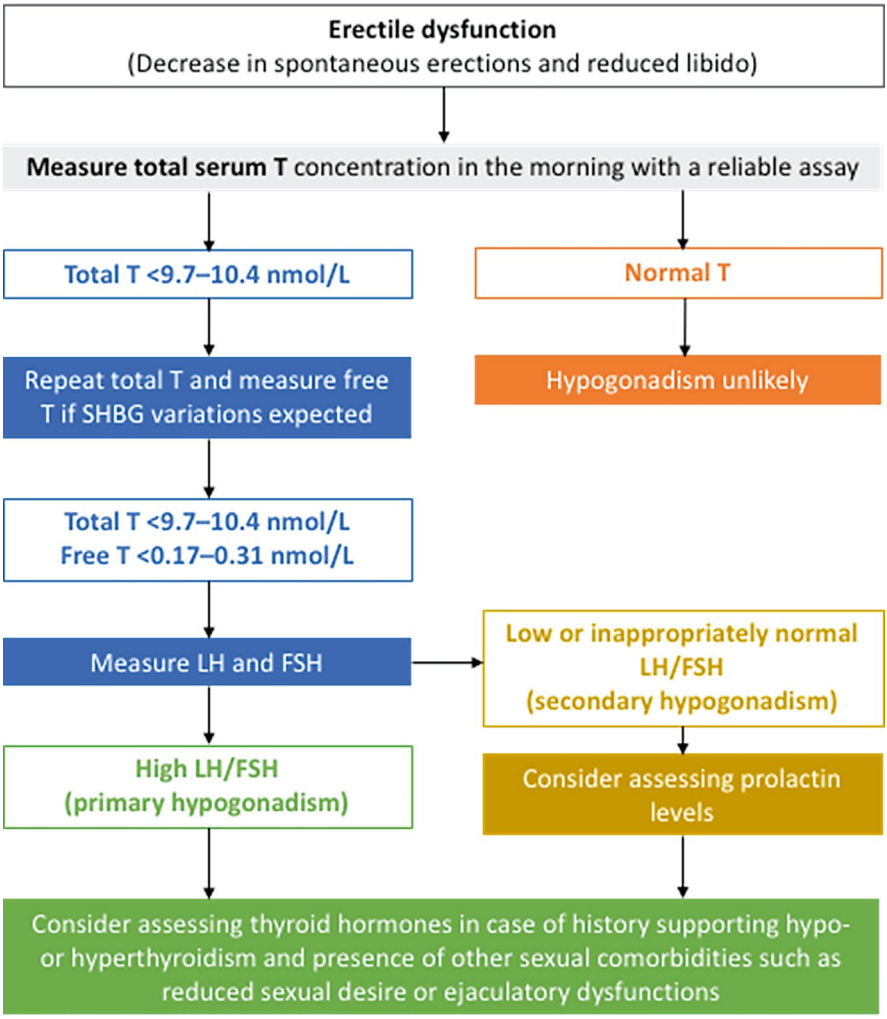


**Fig. 6.3** Diagram of a potential screening approach for endocrine pathologies (ED) in patients presenting with erectile dysfunction. The approach to endocrinological assessment of the patient presenting with ED should focus on the initial assessment of testosterone (T), the results of which then guide 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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# From the Manichean Dichotomy, Through the Biopsychosocial Model, to Systems Sexology, the Final Evolution of Sexual Medicine

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**Abstract**

Over time, the conceptualisation of erectile dysfunction (ED) and the approaches to its treatment have changed considerably. However, there remains an important need to challenge the Manichean dichotomy of viewing ED as either *psychogenic* (arising from the mind) or *organic* (biological) in nature. This chapter provides an overview of the evolution of sexual medicine throughout the past centuries, highlighting key paradigm shifts in the understanding of sexual dysfunctions, including ED. Through an analysis of the praiseworthy but sometimes overused biopsychosocial model, the Manichean or dichotomous approach to diagnosis and the modern systems sexology (SS) perspective, we argue that the term psychogenic is not only redundant in modern practice but is also an affront to the progress made in sexual medicine, potentially harming patients, research, and the entire field. A SS approach is needed to integrate the effects of the systems of mind, body, experiences and society to understand how they produce sexual health or sexual dysfunctions, such as ED. Thanks to this innovative perspective, clinicians can fully understand how sexual health is a powerful and effective biomarker of overall health, just like the famous canary in the coalmine, which warns early that something is wrong and risks are developing. Thanks to SS, we can clearly understand the identity between sexual medicine (SM) and systems medicine (SM), the part of internal medicine dedicated to non-communicable chronic diseases. The two SMs recognize lifestyles, dramatically influenced by culture and subculture, society and the choices (or inchoate choices) of governments and economists, as a primary risk factor, with the

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same inflammatory mechanism, of sexual dysfunctions. Thus, SM+SM=SS is not a mere equation or a play on words, but an effective tool for increasing sexual health, an essential and indispensable part of the overall health of humanity.

**Keywords**

Manichean · Dualism · Biopsychosocial · Systems sexology · Systems medicine · Erectile dysfunction

## 7.1 Evolving Treatment Paradigms in Relation to ED

Erectile dysfunction (ED) has been recognised as a health condition for millennia. Throughout history, there have been numerous attempts to understand the underlying causes of ED and understand optimal treatment approaches for this sexual symptom [1]. A brief history of the progress made in Western science in understanding erectile function, and dysfunction, is presented as a road map to the current evolution of the new, hectic field of sexual medicine.

In Ancient Greece and for centuries thereafter, it was believed that erectile function was driven by *pneuma* (meaning 'breath' or life force) entering the penis [2]. Hippocrates recognised the influence of *pneuma* flowing into the penis and advocated for a balance of the four humours in promoting adequate erectile function. Both Hippocrates and Aristotle held the view that the testes were a fulcrum of sorts, with a pulley system linked to erectile function [2]. Aristotle ascribed successful erection to three mechanisms: imagination; moisture (which increases subsequent to pneuma in the penis) and the fulcrum action of the testes.

The view that air entry into the penis caused erections was not sufficiently questioned until the insights of Leonardo da Vinci. Da Vinci famously attended a public hanging and observed a dissection of the hanged man, in which the erect penis was filled with blood, which inspired his attempt to describe the anatomy and physiology of erection (Fig. 7.1).

However, such observations appear to have been overlooked in professional sciences until Ambroise Paré made similar assertions a century later [2, 5]. It was not until the seventeenth century that the mechanism of blood influx into the penis was demonstrated physiologically as a driver of erectile function. It took a further century to recognise the influence of the nervous system on penile blood flow and even longer to elucidate the mechanisms through which blood flow was controlled in tumescence and detumescence. Only in the late twentieth century were the mechanisms of arterial dilation under neurological, vascular and hormonal control understood to a significant degree [2].

In parallel to the anatomical and physiological advances in understanding erectile function, strategies to manage ED were proposed [6]. Many of these followed the evolving understanding of the mechanical control of penile function, including the use of vacuum erection devices, first developed in the 1800s, to encourage penile blood flow [7]. However, there was equally an emphasis on spiritual therapies, reflecting the ignorance of biological mechanisms linked to ED, including talisman use in Ancient Greece, the use of aphrodisiac compounds or food and the

**Fig. 7.1** *The Coition of a Hemisected Man and Woman* by Leonardo da Vinci. Probably in the same year that Colombus discovered the New World—in 1492—another Italian drew this unique picture. The depiction of sexual intercourse was drawn by Leonardo with some errors, such as the sperm originating in the spinal column, instead of the testicles, and travelling from there to the penis. It also incorrectly depicts two separate channels for urine and semen. The position of the testicles and breasts suggests that the intercourse described was not in a horizontal position, such as the missionary position, but in the standing one. Moreover, despite the exquisite interest in female beauty, the woman is only represented by her cavities—there is no face or head or torso [3]. The frequent drawing of anuses and penises found among his notes, and its celibacy are elements suggesting that da Vinci had a sexual interest in males. Indeed, in 1476, he was arrested by the *Office of the Night* (a kind of moral policing unit in Florence) under the accusation of sodomy [4]. (Image used with permission © Royal Collection Enterprises Limited 2025 | Royal Collection Trust)

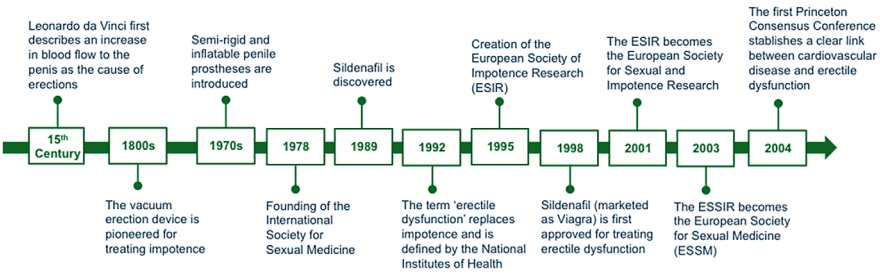


**Fig. 7.2** Timeline of recent historical developments relating to sexual medicine and erectile dysfunction [8, 12–14]

consumption of animal penises or seminal fluid [6]. As an understanding of the role of hormones, particularly testosterone, emerged in science and medicine, attempts to increase androgen levels to remedy ED were also attempted. However, progress in the biological management of ED was slow despite some advances in scientific knowledge, limiting medical treatment options.

In contrast to the pursuit of therapies relating to the biomedical features of erectile function, psychological therapies emerged as a key treatment paradigm in the early twentieth century. The psychoanalytic approach of Freud, among others, established an approach to ED that ascribed sexual dysfunctions to the psyche of the individual patient and largely persisted throughout the century [8]. Psychoanalysis then gave way to cognitive behavioural strategies that aligned with a broader shift towards a greater appreciation of biological, social and psychological aspects of illness in the 1970s [9]. Finally, the development of sildenafil, the first phosphodiesterase type 5 inhibitor, led to a new paradigm where the pharmacological treatment of ED dominated, largely replacing psychoanalytical and cognitive behavioural approaches. This resulted in the substitution of the previous psychological *reductionism* ('it is all in your head') with the medical one ('it is all in a pill') [8]. The current perspective aims to integrate the strength of medical treatments with the power of counselling and, in selected cases, of psychotherapies [10].

The history of how ED has been conceptualised and managed is evidently circuitous, reflecting advances and missteps in scientific exploration and crossing the boundaries of physiological/anatomical, psychoanalytical and psychological treatments, up to the dominance of pharmacotherapy today. Figure 7.2 illustrates recent milestones in the history of sexual medicine and ED management that are of relevance to current practitioners. Importantly, treatment strategies evolve in line with changes in how the causes of ED are conceptualised in the context of broader changes in overarching health theory [11, 12]. As noted in the previous chapters of this book, there is a strong link between ED and the onset of non-communicable diseases (NCDs), with ED potentially serving as a marker (the *canary in the coal mine*) for these conditions. As our understanding of NCDs has evolved to appreciate the role of not only biological but also cultural, psychological, societal and environmental factors in their development, such understanding should be applied to ED. Consideration of the complexities underlying the development of ED through the prism of NCD diagnosis and treatment has the potential to inform more integrated treatment approaches.

In this chapter, we focus on three paradigms that have been applied to the diagnosis and management of ED—to represent all sexual dysfunctions: the **Manichean dichotomy**, the **biopsychosocial** (BPS) **model** and the emerging paradigm of the **systems sexology** (SS), which we suggest as an evolution of our understanding of ED as a complex condition. We argue that the Manichean dichotomy approach is a redundant strategy when applied to the diagnosis and management of ED (as well as wider sexual dysfunctions). While the BPS model has benefits over the dichotomous model, this is also argued to have some limitations in the context of sexual medicine. Finally, we assert the thesis statement that the progression of sexual medicine from the simplistic Manichean dichotomy to the comprehensive SS approach has major advantages for both patients and clinicians.

## 7.2 The Manichean Dichotomy and the Exclusion Diagnosis in ED

The Manichean dichotomy reflects a fundamental emphasis on dualism when facing reality [15]. The term stems from the Manicheism religion, where there is a distinct emphasis on the duality of light/darkness and good/evil when viewing the world [16]. While that religion has now been consigned to history, the fundamental view of separate and contrasting entities serving as influences over life remains common across belief systems and even within the history of medicine. When applied to medical illness, the dualism of mind-body proposed by Descartes is a prime example of how Manichean dichotomies may influence scientific thought and even medical behaviours. Descartes proposed a separation of mind and body in the seventeenth century as a response to the dominant Christian view of mind-body connection and the impact this had on an understanding of illness and disease [17]. As the body and soul were viewed as one, illness was often ascribed to actions that went against moral values or wrongdoings on a social level. By promoting a dualism of the mind and body, the French philosopher opened the door for a positivistic natural science, where analytical methods could be applied to medicine [17]. By isolating the body as a physical, biological entity, this allowed for the expansion of the investigation of disease as a deviation from normal physiology and anatomy, without the need to integrate such assertions with the mind.

Over time, this avenue of scientific investigation bore substantial fruit and led to a biomedical model of illness, which remains embedded in modern biomedical sciences. One of the consequences of this development was that there was an overcorrection and emphasis placed on biological factors, without consideration of the potential interaction or modulation of those factors through mental processes or experiences or the environment. Thus, the dualistic approach denied the mind's role in the experience of health, distorted an understanding of human beings through obsessive measurement and quantification and did not allow for the inclusion of psychosocial or spiritual aspects in human health experiences [18].

One of the main challenges to emerge from this approach was the delineation of disease as organic or psychogenic. *Organic* (from the Oxford Advanced American Dictionary: 'connected with the organs of the body') is used to individuate the physical, such as the molecular origin of health and diseases, in contrast to the term

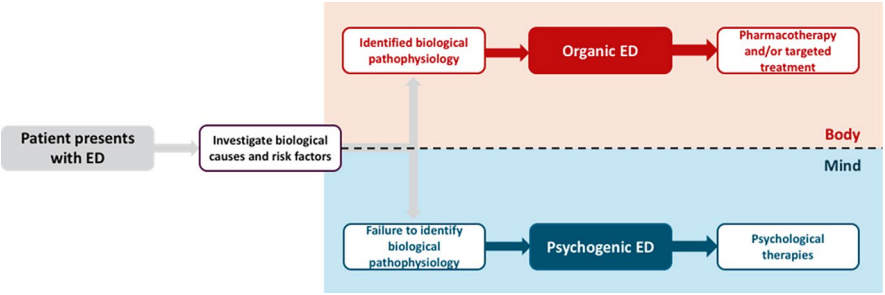


**Fig. 7.3** Illustration of the Manichean dichotomy when applied to the diagnosis of erectile dysfunction [15, 20]

*psychogenic* (from Ancient Greek: 'psyché', mind plus 'ghénos' origin), which implies that a pathogenetic mechanism is (exclusively) generated by the mind. Unfortunately, the label psychogenic is still very frequently employed in conditions where no obvious organic cause could be found [19]. In fact, psychogenic became a term used to define a **diagnosis of exclusion** (*if I am unable to find an organic cause, the sexual symptom must be psychogenic*) and one that implied the lack of a clear, rational underlying cause for symptoms [20, 21]. The use of such a label has been noted in a range of apparently **idiopathic** conditions, including chronic pain, psychiatric conditions and pathologies affecting sexual function, such as ED (Fig. 7.3). Indeed, until recently, the term psychogenic has been employed in the diagnosis of ED where an overwhelming psychological component was believed to be present without a clear organic cause [15, 19, 22].

Although so dramatically popular that it produces >900 entries in PubMed and is considered the diagnostic standard of several guidelines produced in the Anglo-Saxon environment, [23, 24], the Manichean dichotomy is a problematic approach to ED for many reasons. Firstly, the dichotomy does not take into account the interactions of multiple factors driving the development and persistence of ED, which has been amply demonstrated in the wider literature and within the chapters of this book [15, 19]. Rather than providing a useful framework for separating ED into specific sub-types that can guide future treatment [24], the separation of psychogenic and organic ED is artificial in nature. This separation reflects (i) an attempt to oversimplify the complex nature of ED, (ii) the search for a unique aetiology for a symptom that typically recognises multiple risk factors, and (iii) a lack of integration of the multitude of factors influencing ED development and may have damaging effects on patients. A demonstration of the ability of a Manichean posture to generate monsters is provided by studies of nocturnal penile tumescence and rigidity, with and without the aid of a computerized recording device (Rigiscan), which have traditionally been placed at the top of various ED diagnostic flowcharts with the aim of distinguishing between psychogenic and organic etiologies [25]. The idea was very rudimentary, unsupported by robust scientific evidence, but at the same time it was highly successful, at least in surgical environments inappropriately trained to provide simple solutions to complex problems: if a patient has good erections for three consecutive nights while suffering from ED during sexual

intercourse, his problem cannot be physical in nature. Although Rigiscan can be a valuable aid in supporting the diagnosis (but still unable to identify any cause or risk factor for ED) and in verifying the presence and intensity of erections in particular research contexts [26], since several conditions can produce false positive and false negative results, its use as the sole tool in the diagnosis of ED is completely incongrous and even capable of producing dangerous diagnostic errors [27].The consequence of this posture is to deny to those with a diagnosis of 'psychogenic' ED, but with biological risk factors, the opportunity to receive counselling on prevention and appropriate medical treatments. Moreover, it may also serve to dismiss ED as a manifestation of the patient's mind (which in itself may perpetuate ED and drive negative psychological outcomes) [28]. On the other hand, very frequently, a patient diagnosed with a 'purely' organic ED is treated with drugs without any attempt to establish and manage the comorbid psychological aspects of its ED.

We argue that the Manichean dichotomy and the concept of mind-body dualism are obsolete in clinical practice and that the term psychogenic is redundant, abusive, stigmatizing, risky, and able to generate pleanty of diagnostic and therapeutic mistakes (Table 7.1).

Arguments against a diagnosis of exclusion are numerous and underscore the importance of psychological factors in driving ED, which often co-occur with biological factors, as risk factors and/or consequences of the sexual dysfunction, including risk factors for cardiovascular disease [29]. There is a need for a deeper

**Table 7.1** Why the label psychogenic cannot be used in sexual medicine anymore

| | |
|---|---|
| … because the term psychogenic is *redundant* | All sexual dysfunctions are impacting the mind. There is no need to specify that a given ED case is psychogenic. All sexual dysfunctions are "psychogenic", and all sexual dysfunctions need a psychological assessment, at least during the irreplaceable phase of the counselling |
| … because the term psychogenic is *abusive* | The term psychogenic means 'generated by the mind'. However, there are no instruments or psychometric tools that can demonstrate a doubtless causative role of the mind in a given case of ED |
| … because the term psychogenic is *stigmatising* | The patient can easily understand the label psychogenic as a psychiatric diagnosis or a hopeless need for never-ending psychotherapy |
| … because the term psychogenic is *risky* | Several flow charts, guidelines and doctors suggest psychotherapy for patients labelled as psychogenic, but without evidence of the possible outcomes and with the risk of increased anxiety and depressive comorbidities in the case of therapeutic failures |
| … because the term psychogenic cannot be the consequence of an *exclusion* diagnosis | The use of exclusion-based diagnosis in ED is nonsense. The idea that, at the present moment, medicine has all the possible diagnostic tools for excluding all possible causes of ED is, at best, rudimental and pre-scientific |
| … because the term psychogenic produces therapeutic monsters and tragic *mistakes* | The idea that "psychogenic" patients should be treated through psychotherapy and those with organic ED should be treated with drugs is far removed from evidence-based medicine. In fact, many patients with ED associated with psychorelational or social risk factors will benefit from pharmacological treatment; similarly, the majority of patients with an organic risk factor (e.g., diabetes) will certainly have better outcomes if medical or surgical therapy is combined with talk therapy |

understanding of the complexity and wider factors that contribute to ED rather than a reductionist approach to ED classification and evaluation.

Another dramatic consequence of the use of the term psychogenic is the automatic referral of those patients to the 'hell' (as frequently perceived by the patient) of never-ending psychotherapy with unpredictable outcomes, while those with an organic ED may take advantage of physical treatment, such as that with the 'paradisiac' PDE5i [20, 30]. Evidence over the past half-century, drawn from a very large number of studies, has shown that patients with non-organic ED are very well treated with drugs and/or given physical treatments. The power of **sildenafil**, for example, in reducing anxiety and depression in ED patients is comparable in its efficacy to the best psychotherapies, though its effect is much faster, and, likely, more powerful [31, 32]. Interestingly, the anxiolytic and antidepressant power of sildenafil has also been found in pre-clinical models [33–35]. At the same time, it has been well demonstrated that the efficacy of all potentially successful medical treatments for ED is dramatically reduced when the patient is managed in a pill-only setting, without counselling and without any psycho-sexological support [36, 37]. Avoiding the Manichean perspective in sexual medicine means reducing the risk of both psychological and medical reductionism [38].

Finally, as largely discussed in many chapters of this book, in up to 90–95% of cases of the most common cardiovascular symptom—i.e. **hypertension**—it is not possible to find organic aetiologies, yet these patients are not labelled as affected by psychogenic hypertension. However, in the very large majority of hypertension cases, it is easy to recognise environmental, intra-psychic, relational and physical risk factors, ranging from genetics to depression, from anxiety to dyslipidaemia and from economic/job concerns to diabesity. Medicine labels all these cases of hypertension as *idiopathic* (having an unknown cause) but, at the same time, addresses psychological and physical risk factors without any Manichean need to establish if they are organic or not.

It is inexplicable, if not admitting an embarrassing inability to reasoning and an incapacity to renounce the inveterate **principle of authority**, i.e. to the grotesque and dogmatic *Ipse dixit* (Lat. for "he said it himself") [39], why sexual medicine is still marking a number of patients with the infamous and illegal label of psychogenic instead of idiopathic, as is universally done for other more diffuse symptoms.

## 7.3 The Biopsychosocial Model in Relation to ED

The BPS model was proposed by George Engel in the late 1970s as an alternative to the prevailing biomedical model of care in medicine [40]. It arose from perceived limitations of the biomedical model, including a lack of appreciation of the person who has the illness, failure to take into account the person's experience and attitude towards complaints, care of the patient as a person and the wider social factors that determine how a health condition may be conceptualised [40, 41]. This model represented a shift from perceiving health as the absence of illness to understanding both illness and patienthood in the context of health [40].

The BPS model incorporates three elements that have distinct features but also overlap when considering the health of a patient: *biological* (genetics, physiology and pathology), *psychological* (thoughts, emotions, experiences and behaviours) and *social* (relational, socio-economic, cultural and environmental) [40]. At the time of the development of this model, there was an increasing recognition of the importance of social factors and wider determinants of health that could influence a range of conditions. While the model initially emerged as a mechanism for improving psychiatric and psychological treatment, which was heavily centred on psychological theory and aetiological assumptions, its broader application to all medical conditions has been seen over time [42]. Hence, the adoption of the BPS model has aligned with prevailing changes in society that emphasise the interconnected nature of health.

The application of the BPS model to sexual dysfunction, including ED, has been strongly and correctly advocated [42, 43]. Importantly, this paradigm offers an opportunity to capture a diverse range of factors, social, intra-psychic, relational and biological, that can contribute to the development and persistence of ED. A position statement from the European Society of Sexual Medicine [44] asserts the importance of psychosocial variables in the evaluation and diagnosis of ED, promoting the use of the BPS model in complementing existing medically grounded knowledge on this condition. Indeed, there is a wealth of evidence suggesting that intra-psychic, relational and biological factors can exist within the same patient to drive the development of ED [45–47]. Although not always clear to some health care providers, researches, and guidelines writers, the presence of psychopathological elements in a given case of ED could be caused by the erectile failure rather than causing the ED itself. Establishing the causal or causative relationships could be not always essential (or possible) in the diagnosis of ED, as in both cases intrapsychic and relational issues must be addressed and cured.

When assessing a patient with ED, their medical and sexual history is a key element in investigating the potential factors underlying ED that may influence treatment approaches [47]. Adopting the BPS in this context suggests the exploration of key factors related to biological health, mental/psychological health and social, cultural and relational factors. A summary of the BPS applied to ED assessment is presented in Fig. 7.4. The relevance of the BPS model is underscored by the important role of psychosocial assessment in ED, which should include an evaluation of sexual dysfunction; the perceptions of the patient (and their partner); sexual history and skills within the couple; the emotional impact of ED; communication patterns and barriers between the couple; preferences regarding sexual stimulation, including likes and dislikes; and beliefs about sexual performance [44]. These assessments not only consider the risk factors that contribute to ED but also incorporate elements of social/relational and psychological influences that may create conditions favouring the development and maintenance of ED. This also recognises that ED is not a condition that uniquely affects the patient in isolation but rather a socially positioned phenomenon. Recognising these factors at the diagnosis and assessment phase may have important implications for the management of ED, including the adoption of strategies such as psychoeducation, couple therapies and communication skill development, alongside medical therapy, as indicated [44].

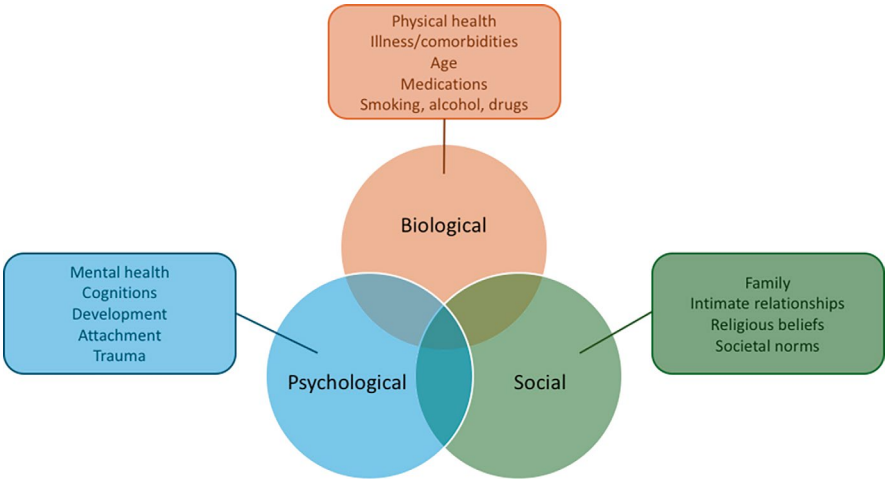


**Fig. 7.4** The biopsychosocial model of health and key links to erectile dysfunction. This diagram illustrates the range of biological, psychological and social factors that influence erectile dysfunction [47, 48]

Importantly, the use of the BPS model entails a collaboration of multiple professionals during the assessment of ED to adequately evaluate and manage identified causative factors [44]. The benefits of the BPS approach in this context also align with the use of a patient-centred, holistic focus that can have positive effects on the experiences of the patient, as well as on future treatment outcomes. For instance, it has been shown that patient-centred approaches to sexual medicine led to increased satisfaction with healthcare services and the outcomes of consultations [49]. Patients are also more likely to collaborate with clinicians when care is patient centred, allowing individual needs, expectations and ideas to be explored and addressed [50]. Consequently, the BPS model has become a recommended approach to delivering holistic care and pursuing more diversity, inclusivity and integration when deciding on treatments and evaluating their outcomes [44].

While there are merits to the use of the BPS model as a conceptual framework for understanding ED and diagnosing and assessing this condition, there are also pitfalls when a conception of sexual health includes only biological, psychological and social factors. One of the main limitations of the BPS model in sexual medicine is the lack of real attention paid to the sociocultural factors involved in sexual expressions [43], despite the "declaration of interest" in the social aspects of sexuality. For instance, in the clinical research, the role of negative attitudes towards sexuality within societies and political regimens, the impact of healthcare systems and interactions and the influence of occupation/employment on sexuality and sexual function are not fully captured by the authors inspired by the BPS model. This reflects the dominant focus on factors that directly influence the individual rather than reflecting wider spheres of influence that may have shaped the development of sexual attitudes and behaviours. While the BPS perspective officially attempts to capture the importance of social interactions and cultural or relational factors to some extent, these are often considered superficially or in relation to specific

experiences rather than as forces that shape sexual function. Looking at the scientific production inspired by the BPS model, it is evident that psychologists mainly deal with psychological aspects and urologists focus on the physical failures, with a quite weak interest, or sufficient culture, knowledge and education, in the sociocultural, political, and economic aspects of sexuality. One might not be too far from the truth when stating that many interpreters of the BPS model are in reality granite-like dualistic in their mentality and clinical approach.

Another criticism of the BPS model when applied to sexual medicine is the limited attention paid to the desires, needs and values of the individual patient [43]. In addition, the appreciation of pleasures and the diversities within sexuality are not always included, which may limit the depth of evaluation in patients with ED. Indeed, the specific factors linked to sexual desire in men or the diversities within sexual desire may not be completely understood using the three elements of the BPS model, which ascribe desire to drive (biological), motivation (psychological) and wish (social/cultural) [51]. Consequently, while the BPS model may expand the avenues for exploring the underlying risk factors of ED compared with biomedical models, it may still have limitations around reflecting diversity in sexual desire and function [43, 51, 52].

In conclusion, the BPS model would be excellent but is too often used *uncritically* and as an **alibi** to mask a still rigidly binary approach: psychological or medical or, at best, psycho-medical, with very little attention to social, cultural, political and economic aspects that dramatically impact human sexual health. Often, in fact, the same supporters of the BPS model firmly believe that sexual dysfunctions have to be classified as psychogenic, organic or mixed. Often, the same supporters of the BPS model firmly believe that when a patient is *apparently* not presenting with physical aetiologies, his ED must be considered psychogenic. Often, the same supporters of the BPS model firmly believe that psychotherapy is the elective therapy for patients with psychological weakness (forgetting the powerful 'psychotherapeutic' effect of a well-conducted medical or surgical therapies) or that pills are the elective therapy for patients with organic risk factors (forgetting that all sexual dysfunctions impact the mind, relationships and the social posture of the individual, and deserve counselling if not psychotherapies). As discussed above, those are dramatic, but widespread, mistakes.

## 7.4 Systems Sexology and Erectile Dysfunction

The focus of this section is on defining the SS model and how this may be applied to the diagnosis of ED. To appreciate this innovative perspective, it is necessary to recall the **bioecological systems theory** (BST) proposed by Bronfenbrenner [53]. The BST was a development of the ecological systems theory, which asserted that human development is the product of reciprocal interactions between multiple systems, including the microsystem, mesosystem, exosystem, macrosystem and chronosystem [54]. Within this model, the *microsystem* includes the closest relationships that an individual may have (e.g. family, friends and partners) as well as biological influences on the individual. When microsystems interact, this is captured within

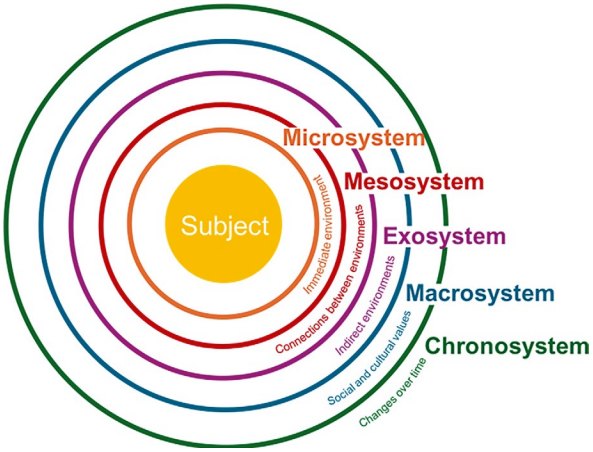


**Fig. 7.5** Representation of the Bronfenbrenner's ecological theory. This theory highlights the hierarchical influence of different systems and their impact on the individual subject, including the immediate environment (microsystem), interactions between environments (mesosystem), indirect environments (exosystem), social and cultural values (macrosystem) and the changes that may occur over time (chronosystem). (Adapted from reference [53])

the *mesosystem*, a collection of interacting microsystems that may influence the life of an individual. The *exosystem* includes influences that may not be part of the immediate environment of the individual but result from institutions that may be influential, including schools, healthcare, media and the community. The *macrosystem* captures larger systems in society, such as religious, cultural and societal influences on health and well-being. Finally, the *chronosystem* represents changes over time, which may include changes in relationships or experiences. The expansion of this model to incorporate biological processes led to the development of the BST (Fig. 7.5) [53].

It is important to re-emphasise that sexual function in humans perfectly fits the idea of this ecological theory. Besides all the individual factors, sex is affected by continuous interactions within a multi-level system (for example, enjoying sex under religious perspectives, differences between Western vs. Eastern cultural contexts, etc.), and it is largely affected by historical factors, such as awareness of the possibility to be treated for ED, i.e. the *Viagra Revolution*; the diffusion of the Internet; and the emergence of the 'abilities' of so-called *Dr. Google* or artificial intelligence.

Why is it important to consider ED as a consequence of systems of influence rather than by adopting a discrete model such as the BPS approach? The importance of this system method lies in its ability to define a vast range of influences on the individual and, of course, the couple as a unit. We argue that the systems philosophy provides a more robust evaluation of the factors that influence health and disease in a given environmental context with respect to the half-century-old BPS model.

Given that a systems medicine approach has been applied to the current conceptualisation of NCDs, it may, therefore, also be applicable to ED [10, 55]. NCDs are recognised to be multi-factorial in origin and arise from a combination of risk factors that may be modifiable, intermediate or non-modifiable. While many NCDs may be strongly linked to modifiable risk factors, such as cigarette smoking and chronic obstructive pulmonary disease, their risk is typically influenced by other environmental factors, including urbanisation, migration, pollution and socio-economic factors [56]. Genetic factors are also recognised as playing a role in the development of NCDs, such as by increasing susceptibility to environmental risk factors and lifestyle risk factors. While NCDs are more common with advanced age, there is increasing evidence that risk may be linked to early perinatal or childhood experiences and exposures [56]. The age at which an NCD develops and the severity of the condition (as well as its impact on the individual) varies considerably from person to person [11]. Therefore, NCDs demonstrate the complexity of gene-environment interactions, socio-economic connections and comorbidities that determine the specific phenotypes experienced by an individual [11].

Hence, the systems approach applied to NCDs appreciates the interaction between the biochemical, behavioural, and environmental domains of health. NCDs may be considered a single expression of disease with different risk factors [56]. The influence of multiple systems on the development of NCDs necessitates an analysis of individual patient data as well as the integration of environmental, biological and clinical data [56]. Such complexity is also evident within sexual medicine, and the development of SS has been suggested as an integrative approach to this discipline [11, 57].

Fundamentally, the SS approach rejuvenates and increases the complexity of the BPS model and applies it to a sexual medicine context [57]. This includes the integration of the BPS model with a **sex-positive approach**, allowing for wider consideration of aspects of sexual desire, differences and variations [43]. Characteristics of the sex-positive approach in SS include respect for sexual and gender expressions, the importance of consent in sexual activity, the recognition of differences in sexual expressions and behaviours and an exquisite understanding of the validity of sexuality in healthcare and education [43]. Sexuality is not just seen in sexual behaviours but also reflects social, historical and wider environmental forces that shape gender identity, values and expressions [58]. Therefore, excluding a broader appreciation of the systems of influence on sexuality and sexual expression may limit the degree to which sexual dysfunctions, such as ED, can be adequately conceptualised.

SS incorporates the complexity of human sexuality, including social, political, cultural, historical, religious, biological, psychological and relational systems. This integrated approach may be applied to sexual dysfunctions, including ED, providing a basis for understanding the development of the condition and the assessment needs of patients [10]. Figure 7.6 illustrates the key elements of SS as applied to the

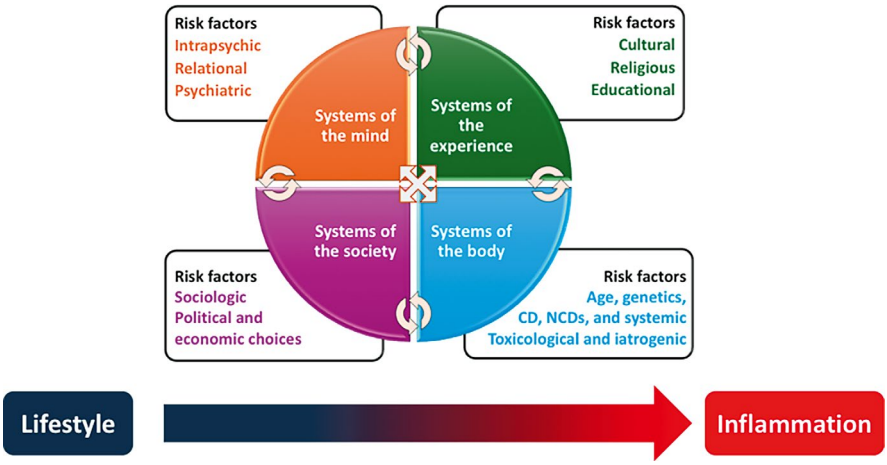


**Fig. 7.6** Diagram of systems sexology as applied to erectile dysfunction evaluation. *Pathogenesis of erectile dysfunction in the light of systems sexology.* Note that the four systems (mind, experience, society and body) deeply influence each other, having the wrong lifestyles as a pathogenetic mechanism and acute, sub-acute and chronic inflammation as a common mechanism of action. Abbreviations: *CD* communicable chronic disease, *CV* cardiovascular, *NCDs* non-communicable diseases

development of ED. This diagram emphasises the importance of lifestyle as a key factor in the development of ED but illustrates the complexity of factors that can influence the potential for lifestyle to drive inflammation as part of the pathogenesis of ED. Notably, there are interactions between all systems within this model, adding complexity to the simplistic idea that the presence of a lifestyle risk factor determines the risk of ED. Rather, lifestyle risk factors may be influenced by a range of systems to increase the risk of developing ED in specific individuals, given their unique circumstances and environment.

Application of the SS model to the diagnosis and assessment of ED should be implemented in the broad approach to patient evaluation and management. For instance, as seen with the BPS model, introducing clinical history and examination elements that explore sexual health and environmental factors linked to the risk of ED may be important in this context. An example of SS assessment questions is presented in Table 7.2. Exploration of factors such as the characteristics of sexual arousal, the influence of relationships on sexual function and the broader influence of school, healthcare, media and society across the lifespan may provide a basis for a more in-depth understanding of the needs of the patient. Therefore, the application of this model to ED represents an inclusive and comprehensive approach to sexual function assessment.

**Table 7.2** Illustrative assessment questions when assessing erectile dysfunction according to the systems sexology model

| System | Questions for patient assessment |
|---|---|
| Body | Do you like your body? Do you believe it is sexy enough?<br>Do you have cardiovascular disease, diabetes or other chronic physical health conditions?<br>Tell me about your lifestyle. (Do you take legal or illegal drugs? Do you smoke? Do you drink alcohol? Do you practise sport? How is your nutrition?)<br>How would you describe your erectile function? How has your erectile function changed over time? |
| Mind | How do you know when you are sexually aroused?<br>Did your parents and caregivers view sexuality as a positive or negative part of life?<br>Did your educators view sexuality as a positive or negative part of life?<br>How have previous sexual relationships influenced your current relationship?<br>How does your current partner(s) impact(s) your erectile function? Which are your partner(s) needs, objectives, and goals? |
| Experience | Was sexual education part of your school experience? How has this shaped your attitudes towards sexual activity?<br>What influence does media (movies, television, music, the internet, socials) have on your expectations of a sexual relationship?<br>Is it acceptable for you to have sexual relationships before marriage?<br>Whom is it okay to be attracted to? What makes an appropriate sexual partner?<br>What is your relationship with the LBGT+ community? |
| Society | How do you perceive your sexual role in relation to your gender?<br>Do worries about money influence your sexual function and sentimental relationships?<br>Do you feel able to express your sexuality in your society?<br>Is the society where you are living a friend or foe of your expression of your sexuality? |

Adapted from reference [57]

## 7.5 Comparison of the Three Paradigms in Terms of Their Conceptual Frameworks and Clinical Implications

The three paradigms discussed in previous sections demonstrate the diverse range of perspectives that can be used to understand the diagnosis and treatment of ED. From a conceptual perspective, the three paradigms reflect different phases of the wider evolution of medical and social thought over time. The Manichean dichotomy may be considered reflective of the dualism that emerged as a consequence of the suppression of medical knowledge development by religious views. While Descartes employed dualism as a means of separating complex components within a system, providing an opportunity to advance biomedical knowledge dramatically, it may not be seen as an over-correction to maintain this dualism. Conceptually, this dualism has led to a separation of the mind from the body in medical disciplines and may be considered damaging to the understanding of the patient as a person within their environment [15].

The emergence of the BPS model represented a shift in the conceptual perspective towards appreciating the person, rather than focusing exclusively on the disease process (the biomedical model). This undeniably has strengths in illustrating health as a holistic combination of factors and not merely the absence of disease [41]. However, it may also be limited when considering the wider factors that influence health, without appreciation of more nuanced factors that can influence health and well-being in an environment and given time. SS adds to the BPS model and emphasises the wider systems that influence health, thus building a more complete – and multifaceted – picture of the factors influencing the general and sexual health of the individual [11]. However, as complexity increases and multiple influences are included, it can be argued that these models become unwieldy in practical application. The time needed to explore these complex systems during a consultation and the uncertain relevance of all factors for the individual patient may pose a barrier to the uptake of such models. This is particularly true where clinicians have a dualistic model of health embedded in their practice, specifically in the field of sexual medicine, as a consequence of clinical training or engrained cultures of practice [59].

A comparison of the clinical implications of these paradigms does suggest that there are benefits to pursuing the more complex SS approach, however (Table 7.3). For instance, these paradigms may have an impact on how healthcare professionals approach ED. The Manichean approach would focus on the categorisation of patients according to psychogenic or organic risk factors for ED and then implementing a treatment course that reflects the outcome of this assessment. This would overlook the interaction between these factors and could preclude effective treatments. For instance, PDE5is have shown efficacy in diagnosed idiopathic and organic ED, suggesting that categorisation in this way may not have a clear benefit to treatment planning [60]. In addition, patients classified as having psychogenic ED may not undergo thorough investigations for biological and lifestyle risk factors, limiting opportunities for the early prevention of NCDs where ED is an early marker [20]. Therefore, the adoption of this paradigm may arguably be damaging to treatment decision-making and could overlook opportunities for wider health promotion. In contrast, the BPS and the evolved SS approaches should provide a more holistic examination of ED, including risk factors and links with the environment, which can guide more effective treatment decisions and opportunities to address wider health issues.

Ultimately, overt or hidden Manichean thinking may have a negative effect on patients, the quality of the care they experience and their outcomes in the context of ED. The benefits of the BPS and the SS approaches include the potential not only to optimise decision-making but also to explore ED within the wider context of health and well-being. When viewing ED as an early marker of NCD (the true *canary in the coalmine*), SS is particularly valuable and may support wider health by allowing consideration of the range of factors linked to sexual, social and general health, as in the fashionable *One Health* perspective.

**Table 7.3** Comparison of paradigms in relation to erectile dysfunction and their clinical implications for diagnosis and treatment

| | Manichean dichotomy model | Biopsychosocial model | Systems sexology model |
|---|---|---|---|
| Conceptual basis | Delineation of psychogenic and organic ED, emphasis on biomedical disease model or on psychological issues. The basis for medical and psychological reductionisms | Largely mentioned and used, but often not completely and integrally. Reflects the patient as a person; biological, psychological and social contributors to health; recognises the interplay between these factors in ED | Holistic but complex perspective. Reflects the importance of systems of influence on health and well-being; recognises ED as multi-factorial and refractory to psychological, medical, and surgical oversimplifications. It is based on the developmental origin of health and diseases |
| Influence on ED diagnosis | ED is categorised according to psychogenic or organic aetiologies | ED diagnosis is nuanced and appreciates the link between factors | ED diagnosis is nuanced, comprehensive and considered across multiple systems |
| Aim of the diagnosis | To find the aetiologies | To identify the aetiologies from a holistic perspective | To identify the specific weight of environmental, psychological, lifestyle and physical risk factors |
| Influence on ED treatment | Psychogenic treatment is separate from organic treatment | Treatment is tailored to the needs of the patient to maximise biological and psychosocial function | Transdisciplinary, multidisciplinary and transcultural. Treatment is tailored to meet the wider needs of the patients in their environment |
| Output of ED treatments | Medical treatments for organic patients, psychotherapy for psychogenic patients | Integration, when possible, of medical and psychological treatments | Intervention on the lifestyles and on the patient's environment. Then, integration of counselling with medical and psychological therapies |
| Strengths | Simple approach to implement | Recognises the interplay between biopsychosocial factors to meet the needs of patient | Comprehensive model; aligned with systems medicine for NCDs. |
| Limitations | Outdated, wrong in the grounding theory, reductionist approach; lacks validity, given the interplay between organic and intra-psychic factors | Limited insight into the sexual desires, needs and values of the patient; fails to appreciate wider systems of influence (media, societal, economic, political, etc.); still affected by the *original sin* of the psychogenic/organic dichotomy, only partially masked by the alibi of the admission of 'mixed' forms, always interpreted as a dualistic mix of the mind and the body | The breadth of the model requires challenging assumptions of sexual health to facilitate practical application |

Abbreviations: *ED* erectile dysfunction, *NCDs* non-communicable diseases

## 7.6 Managing ED in the Light of Systems Sexology

We have argued in this chapter that the diagnosis of ED is a potentially complex process, reflecting a range of factors related to the patient, their environment and their relationships. The Manichean dichotomy, as applied to sexual dysfunction, can be considered obsolete in modern practice. Psychogenic ED does not exist: a complex interplay of the systems of the mind, experience, society, and body is acting in almost every patient with ED. While the use of the BPS model of care can improve upon Manichean thinking when diagnosing ED, providing a greater level of nuance in understanding the causes, contributors and potential sustaining factors of the condition, this too has limitations, as above highlighted.

SS may influence treatment decisions and treatment options considered in patients with ED in a number of ways [10, 43, 61]. As noted within the focused discussion of SS, this model may have an influence on the workup, investigation and needs assessment of patients. This includes a more complete evaluation of the patient as a whole and avoidance of a reductionist approach to categorising ED. This approach has inherent value in guiding the patient in their treatment decisions for their ED and also in supporting the patient in achieving overall health and well-being. For instance, SS may be applied in defining individualised treatment goals for the patient, taking into account their broad context, including sexuality and age. Furthermore, treatment goals may take into consideration the wider needs of a patient in a relationship, involving or not their partner in the ED management [43]. Indeed, the use of a SS approach promotes the active involvement of the patient's partner in both diagnostic and treatment processes. While this is also true of the interpretation of the BPS model when applied to ED [44], the SS model can be considered an advancement of the BPS approach through its inclusion of an extensive set of influences and factors that contribute to health. Whether treatment goals meet the specific needs of individual patients with ED may directly impact their outcomes because of the interconnectedness of sexuality, relationship status and health indicators [61]. The three clinical cases depicted below are representative examples of the SS approach.

*Charles complains of subclinical ED* [62]. *He is unable to get a valid erection when he is with a young and demanding secretary, but when he is having sex with his wife, there are, apparently, no problems. The urologist decided, without any particular diagnostic workup, in a perfectly orthodox Manichean perspective, that the problem is without a doubt psychogenic and suggested personal psychotherapy and/or marital therapy for the husband and wife. After almost 3 years of psychodynamic therapy, the patient sought a second opinion, having seen some improvement in hysterical traits and anxiety but no change in erectile function during his extra-pair relationships. In a more in-depth consultation, the dynamic penile Doppler demonstrated a 20% reduction in blood flow, likely related to the unhealthy lifestyle of Charles. The conclusion of the expert in SS was that Charles was able to compensate for the vascular damage in a non-stressful environment (at home) but not in a stressful and demanding setting (with the mistress). In keeping with the SS perspective, Charles underwent a re-educational programme focused on lifestyle factors, 3–4 h of counselling to discuss myths and sexual expectations and even non-judgmental discussion of the ethical and social aspects of his sexual life, and he was prescribed a*

*discreet form of sildenafil 50 mg, such as the orodispersible film* [63]*, which, being temperature stable, could be carried in the pocket and used without water when engaged in a more complex affair with respect to the matrimonial routine.*

*Luke has well-compensated type 1 diabetes mellitus, but his disease was sufficient to warrant a diagnosis of organic ED due to his inability to successfully penetrate his girlfriend. The diabetologist treated the patient with 5 mg of tadalafil daily, followed by on-demand tadalafil 20 mg before sexual intercourse, and then vardenafil 20 mg. All of these regimens proved unsuccessful in improving sexual function. The expert in SS, who has been consulted after 1 year of useless treatments, discussed with Luke his sexual orientation, also by using a new dedicated powerful psychometric tool, genuinely inspired by the SS, named XYGO* [64]*. This led to the discovery of Luke's hidden same-sex inclination, which he never practised because of the homophobic Mediterranean environment in which he lives. A short psychotherapy course was undertaken to help shift his egodystonic orientation toward an egosyntonic one. The counselling then transitioned to a more liberal environment and was followed by the prescription of low doses of a short-acting PDE5i to be used on demand, mostly at the beginning of a new same-sex relationship. This approach produced an excellent therapeutic outcome.*

*Ambrose is affected by gynaecomastia. He does not have sex because of body shame. During masturbation, the erection hardness score, measured by the Masturbatory Erection Index* [65]*, was below the normal threshold. The endocrinologist discovered normal prolactin and thyroid-stimulating hormone (TSH) levels, total testosterone levels in the low-normal range and slightly higher than normal oestradiol levels. Testicular ultrasound showed both testes to be normal in size and echostructure, while breast ultrasound showed a true but small enlargement of the gland, in addition to increased adipose tissue. Ambrose is living in a heavily polluted environment where pesticides and other endocrine interferents are used daily in his job. He is also an overweight member of the working class and eats junk food almost daily. Changing environment and habits and having a short trial with anti-oestrogens were sufficient to revert gynaecomastia and improve Ambrose's self-confidence. He is now an activist for environmental causes, sharing with his first girlfriend, a vegetarian lady, not only renewed political conscience but also the happiness of sexual health.*

A SS approach allows for consideration of the environment, time, society, gender roles, religion, culture, healthcare, media, school and other systems that may influence ED and is aimed at capitalising on the potential for optimal sexual function among those affected, both individuals and partners. However, to enshrine this model in sexual medicine practice, more needs to be done to challenge dualism and the Manichean dichotomy of psychogenic versus organic ED. We note the importance of ED as an early marker of NCDs as a key driver of the adoption of this model. This may be achieved by aligning the evaluation and management of ED with the systems approach seen in NCD care (Fig. 7.7).

Consequently, ED may be identified as a specific condition and can be managed accordingly but may also be recognised as a wider indicator of the health of the patient in their unique environmental context, prompting wider investigations, preventative strategies and the treatment of NCDs. SS is therefore integral in realising the role of ED as the canary in the coalmine for NCDs.

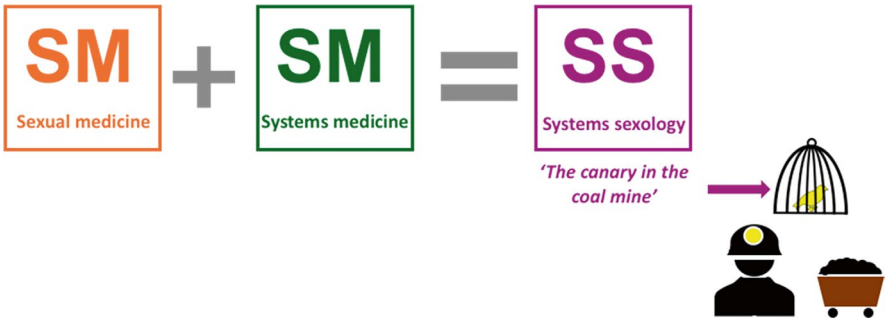


**Fig. 7.7** The SM + SM = SS equation of therapeutic success in erectile dysfunction care. This is the integration of the traditional *sexual medicine* (the first *SM*) with the knowledge of *systems medicine* (the second *SM*) in understanding the developmental origin of health and diseases, recognizing the role of the *four systems* (mind, experience, society and body) and of *lifestyles* in generating the *non-communicable chronic diseases*. In this perspective, sexual dysfunctions in general and erectile dysfunction in particular represent the perfect early *biomarker* of non-communicable chronic diseases as the *canary in the coalmine*

## 7.7 Conclusion

The complexity of human sexuality, its health and its symptoms and diseases has been and still is a challenge for research and clinical practice. After the two steps in the XIX-XX centuries of the psychodynamic-cognitive-behavioural therapies and then of the *Viagra Revolution*, both psychosexology and sexual medicine did not modify their reciprocal posture nor the risk to be prone to the original sins of psychological and medical reductionisms (Fig. 7.8).

In this context, the adoption of the BPS model, despite its holistic original aim, did not really amend the body/mind dichotomy (psychogenic/organic/mixed) almost universally present, like a karst river, in Western sexology. As a consequence, both psychosexology and sexual medicine have been almost universally considered 'Cinderellas' in academic contexts. Despite evidence that sex, in our species, is the driver of a majority of human behaviours and, from a biomedical perspective, the beginning of life itself, despite the exquisite ability of sexual symptoms to work as perfect biomarker of NCDs—the canary in the coalmine, once again—the systematic and official teaching of sexology is overtly ignored in an enormous majority of universities and in psychology and medical schools across the globe [67]. This is due certainly to taboos, ignorance, prejudices and a desire to keep the population less informed about sexual and gender issues, a perverse and pernicious aim of an increasing number of illiberal governments. However, we have to admit that, despite the numerous efforts of many scholars around the world, the field of sexology remains crystallised within the body-mind dichotomy; arrogantly entrenched in defending small patches of psychological, medical or surgical expertise; and, finally, unable to embrace the Socratic *scio nihil scire* (Lat. for "I know that I know nothing") and the Galilean *provando e riprovando* (It. for "trying and trying again" or "proving and disproving"), which are the epistemological bases of any modern

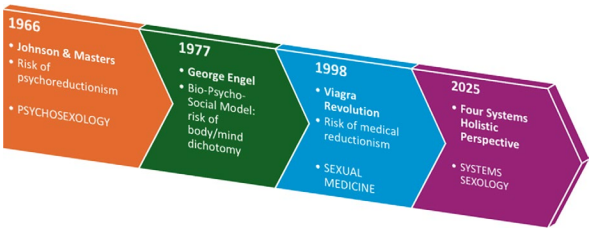


**Fig. 7.8** The timeline of the development of sexual medicine and psychosexology. Four steps could be identified. The first was born from the great exploration of human sexual behaviour, 'normal' and pathological, by Alfred Kinsey and the Johnson & Masters duo [66]. On the one hand, this constituted the foundation of scientific exploration in sexology, but on the other hand, it produced a *psychosexology* that was not always attentive to the scientific method and was always firmly anchored to the mind/body dichotomy postulated in the 1960s. The intervention of the *bio-psycho-social model* did not always improve the patients' prospect of being diagnosed and treated with a truly holistic vision. The *Viagra Revolution* was then the brilliant and highly effective solution to one of the most serious sexual problems of the *boneless* humanity (see the first chapter of this book) but also at the basis of the birth of *sexual medicine*, a medical discipline, but largely cultivated by surgeons, frequently producing a dramatic *medical reductionism*. The time has come to renew our paradigm with the borderless vision of SS that considers the *four fully integrated systems* that make up human sexuality and sexual identity: that of the mind, that of experience, that of society and that of the body. Note that SS is postulated not as a new discipline but as a method for studying human sexuality and as a tool to improve and renew the 'old' bio-psycho-social approach in the interest of patients' sexual health

scientific thought. We therefore strongly agree with Perelman and colleagues who, with intelligence, experience and competence, recently found that <<too many sex therapists and sexual medicine experts claim to adopt the [BPS] model while merely paying it lip service>> [68].

It is time now for a new paradigm, and we propose here a truly holistic one — the SS — in the interest of fruitful research, of the universal teaching of human sexuality and its diseases in the undergraduated and postgraduated shools, and of the sexual and general health of humanity.

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