Gaps in the management of diabetes in Asia: A need for improved awareness and strategies in men’s sexual health

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INTRODUCTION
Traditionally, men’s health has always been associated with male sexual concerns, but it has now evolved and encompasses (1) male gender-specific diseases; (2) non-gender-specific diseases that impact males such as non-communicable diseases and malignancies; (3) male behavior that imposes an increased health risk such as smoking and substance abuse. The European Men’s Health Forum defined men’s health as ‘a male health issue arising from physiological, psychological, social, cultural or environmental factors that have a specific impact on boys or men and/or where particular interventions are required for boys or men in order to achieve improvements in health and well-being at either the individual or the population level’. In this review, we shall focus on the sexual health of males living with diabetes, particularly in Asia.

Sexual health is an important factor of men’s health. Sound sexual health includes the ability to have good erectile function and sexual desire, and it is not merely the absence of disease. Male sexual dysfunction is defined as ‘difficulty during any stage of the sexual encounter that prevents or impairs the individual or couple from enjoying sexual activity’, is globally prevalent in males with prediabetes and diabetes. It is an early harbinger of cardiovascular diseases and has a profound impact on one’s physical, mental, and social health. Among patients with either prediabetes or diabetes, the most common male sexual dysfunctions are hypogonadism, erectile dysfunction, and premature ejaculation. In Asia, although sexual health is an important factor of men’s health, it is rarely discussed freely in real-life practice. Addressing sexual health in Asian males has always been challenging with multiple barriers at the levels of patients and health care providers. Therefore, the assessment and management of sexual dysfunction in routine clinical practice should involve a holistic approach with effective patient–provider communication. In this review, we discuss the epidemiology, pathophysiology, and the management of hypogonadism, erectile dysfunction, and premature ejaculation among males with either prediabetes or diabetes (type 1 and type 2), as well as the evidence gaps across Asia.

ABSTRACT
Sexual dysfunction, which is defined as ‘difficulty during any stage of the sexual encounter that prevents or impairs the individual or couple from enjoying sexual activity’, is globally prevalent in males with prediabetes and diabetes. It is an early harbinger of cardiovascular diseases and has a profound impact on one’s physical, mental, and social health. Among patients with either prediabetes or diabetes, the most common male sexual dysfunctions are hypogonadism, erectile dysfunction, and premature ejaculation. In Asia, although sexual health is an important factor of men’s health, it is rarely discussed freely in real-life practice. Addressing sexual health in Asian males has always been challenging with multiple barriers at the levels of patients and health care providers. Therefore, the assessment and management of sexual dysfunction in routine clinical practice should involve a holistic approach with effective patient–provider communication. In this review, we discuss the epidemiology, pathophysiology, and the management of hypogonadism, erectile dysfunction, and premature ejaculation among males with either prediabetes or diabetes (type 1 and type 2), as well as the evidence gaps across Asia.

As with other diabetes-related complications, sexual dysfunction is prevalent worldwide in males living with diabetes, yet this problem is rarely addressed by health care providers (Figure 1). In Asia, this condition is often overlooked due to fear of embarrassment, cultural sensitivity, and the barriers faced by healthcare providers. This review aims to discuss the epidemiology, pathophysiology, and management of reproductive and sexual functions, but it also leads to a poor relationship of the couple, psychological well-being, and the quality of life.

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SEXUAL DYSFUNCTION

Hypogonadism
Male hypogonadism is a state of androgen deficiency where there is the presence of clinical and biochemical evidence of low testosterone levels (<12.1 nmol/L). Blood samples should be obtained before 11 a.m. while fasting, and two measurements of low testosterone are required to establish the diagnosis. A decline in testosterone levels can manifest with various clinical presentations due to its universal role in the regulation of male physiology such as gonadal function, mood and behavior, muscle mass, lipid, bone formation, erythropoiesis, and immune function.

The prevalence of hypogonadism in males with prediabetes ranges between 30% and 40%. There is a significant inverse association between prediabetes and the total testosterone/sex hormone binding globulin (SHBG) levels after adjustment for age, ethnicity and adiposity. Males with prediabetes had an increased risk of hypogonadism with more severe sexual and depressive symptoms compared to healthy individuals from similar age groups.

Up to 66% of males with type 2 diabetes are reported to have low testosterone levels. Literature reported significant inverse associations between testosterone levels and age, obesity, insulin resistance, duration of diabetes, HbA1C, and the presence of diabetes-related complications. However, evidence of type 1 diabetes and hypogonadism is lacking. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complication (DCCT/EDIC) cohort, the reported prevalence was only 9.5%.

Hypogonadism in males with type 2 diabetes can be explained by a defective hypothalamic-pituitary-gonadal axis (HPA). Although the exact pathophysiology remains multifactorial, several studies reported that suppression of the HPA axis is primarily contributed by insulin resistance and increased adiposity. This has been demonstrated by Dhindsa et al., where low testosterone levels have been positively associated among males with diabetes and obesity. Many studies reported a decrease in insulin signaling as a consequence of insulin resistance in the central nervous system. This led to a...
Sexual dysfunction in men with diabetes

Erectile dysfunction

Erectile dysfunction is defined as a failure to achieve and maintain penile erection necessary for sexual activity. Various published literature has established the associations between erectile dysfunction, prediabetes and diabetes (Tables S1–S4). The first report about the link between dysglycemia and the risk of erectile dysfunction was by Corona et al. in 2012, where males with impaired fasting glucose (IFG) had a higher risk of severe erectile dysfunction (hazard ratio [HR] 1.127, 95% CI 1.038–1.223) and reduced penile blood flow (HR 1.293, 95% CI 1.097–1.525). In the SUBITO-DE (sexual dysfunction in newly diagnosed type 2 diabetes male patients) study involving 1,503 males with type 2 diabetes diagnosed within 24 months of enrolment, the prevalence of erectile dysfunction was 43%. Another study in Kuwait showed a 31% prevalence of erectile dysfunction in males with type 2 diabetes diagnosed within 12 months. The reported prevalence of erectile dysfunction among males with type 2 diabetes ranged between 35% and 90%, due to the variations in age, duration of dysglycemia, type of diabetes, and the diagnostic criteria used. Taken together, these findings suggested that the development of erectile dysfunction might have started during prediabetes, similar to that in cardiovascular disease.

Several studies reported that the prevalence of erectile dysfunction in males with type 2 diabetes was positively associated with advancing age, poor glycemic control, increased duration of diabetes, the presence of macro- or microvascular complications, and the presence of comorbidities (anxiety, depression, hypertension, dyslipidemia, or cardiovascular diseases). Given its close association with obesity and cardiovascular disease, erectile dysfunction is often viewed as a clinical manifestation of obstructive sleep apnea syndrome and shares pathophysiological mechanisms such as endothelial dysfunction. Erectile dysfunction is also associated with ethnicity, in which Hispanic males, Asian Indian, and other ethnicities are more likely to develop erectile dysfunction. This can in part be due to the increased prevalence of comorbidities such as dyslipidemia and diabetes. In addition to this, socioeconomic factors also can contribute to the risk of developing erectile dysfunction.

The prevalence of erectile dysfunction was up to 83.6% among males with type 2 diabetes, with the severity of erectile dysfunction increasing with the duration of diabetes. Exercise was reported to be protective. In Korea, males who exercised at least once a week had a lower risk of erectile dysfunction compared with sedentary males (odds ratio [OR] 0.62, 95% CI 0.44–0.89), while increased physical activity level reduced the risk of erectile dysfunction (OR 0.50, 95% CI 0.35–0.71). However, the duration and type of physical activities were not defined. Compared with normal populations, males with either type 1 diabetes or type 2 diabetes were more likely to have more severe refractory erectile dysfunction, resulting in depression and a poorer quality of life.

Epidemiological data on erectile dysfunction in males with type 1 diabetes is limited. Its prevalence ranged between 26% and 35%. A cross-sectional study in Italy showed males with type 1 diabetes were more likely to have erectile dysfunction than those with type 2 diabetes (odds ratio [OR] 0.7, 95% CI 0.6–0.8). Compared with males with type 1 diabetes, the prevalence of erectile dysfunction in males with type 1 diabetes was lower due to a lower BMI with less insulin resistance. Males with type 1 diabetes were more likely to have ED if they had a high BMI (>29 kg/m²) (OR 2.5, 95% CI 1.5–4.1) or actively smoked (OR 1.6, 95% CI 1.1–2.4).

The pathogenesis of erectile dysfunction in males with diabetes is due to cavernosal arterial dysfunction and oxidative stress, leading to reduced synthesis of nitric oxide with vasoconstriction and failure to initiate and maintain erection. It is a complex interplay of vasculopathy, neuropathy, visceral adiposity, insulin resistance, and hypogonadism. The artery size hypothesis suggests that erectile dysfunction and coronary artery disease represent two spectrums of atherosclerosis; smaller penile arteries are involved in erectile dysfunction, whilst larger coronary arteries are generally affected in coronary artery disease. Hence, erectile dysfunction can be a harbinger of cardiovascular disease. Males with type 2 diabetes and erectile dysfunction had increased risk of angiographically verified asymptomatic coronary artery disease (OR 14.8, 95% CI 3.8–56.9). Another study reported that erectile dysfunction was an independent predictor for coronary artery disease in males with type 2 diabetes after a mean follow-up of 4 years (HR 1.58, 95% CI 1.08–2.30).

Premature ejaculation

Premature ejaculation is defined as ‘persistent or recurrent ejaculation with minimal stimulation before, during, or shortly after...
penetration, and before the person wishes it, due to little or no voluntary control, resulting in distress to the patient and/or partner. There is a lack of evidence on premature ejaculation in prediabetes and diabetes. A recent study has reported a positive association between IFG (defined as \( \geq 6.1 \text{ mmol/L} \) or more) and premature ejaculation, evidenced by shorter intravaginal ejaculatory latency time. The prevalence of premature ejaculation in males with diabetes ranged between 37% and 80% in Asian populations. Similarly, a prospective study showed that males with type 2 diabetes and duration of diabetes >10 years were 2.7 times more likely to develop premature ejaculation compared with males with duration of diabetes <5 years. There was also a significant association between premature ejaculation and HbA1c >7% \((P < 0.05)\).

The pathogenesis of premature ejaculation in diabetes is not fully understood. Traditionally, it has been linked to psychogenic factors such as performance anxiety and depression. Neurotransmitters such as serotonin (5-HT) which primarily inhibit ejaculation, are also considered to play an important role in the pathophysiology of premature ejaculation in diabetes. Animal studies showed that serotonin receptors, in particular 5-HT_2C which is shown to suppress ejaculation in rats, were involved in glucose homeostasis, suggesting that there is an interplay between glucose, serotonin transmission, and ejaculation. Hyperglycemia may also impair nitric oxide synthesis with microvascular abnormalities and autonomic dysfunction causing disruption in the control of ejaculation.

Gaps to improving men’s health in males with diabetes

Most males with diabetes rarely proactively seek help for issues about their sexual health. Sexual dysfunction is a sensitive issue and is rarely openly discussed in real-life practice in Asia. There are several reasons why patients are reluctant to divulge their sexual problems such as embarrassment, social taboo, misconception that sexual dysfunction has low medical importance, false perception of no effective treatment for sexual problems, or that the doctor is too young to discuss erectile dysfunction with. In China, sexual health is considered as lewd and it is inappropriate to discuss about one’s sexual behavior. A study in Hong Kong comprising 4,040 males with diabetes showed that 86% of them did not request for treatment for erectile dysfunction due to embarrassment and disease misconceptions. Another study with 603 participants in China showed that 79% males with diabetes had erectile dysfunction but fewer than 10% requested treatment during consultation, although 76% of them expressed the desire to be treated.

In addition, Asian males believe masculinity (defines a man’s role in the society) is a crucial aspect in the society. Masculine health behavior (or ‘manliness’) is often described as being enduring, stoic, and independent. They believed that they needed to portray a masculine health behavior and thus, being dependent on health care providers could demasculinize them. Males with illness who rely on medical practitioners are viewed as ‘weak’ and ‘unmanly’, and seeking medical treatment for a sexual problem is considered as ‘losing face’ or being undignified. Other factors that may influence their health-seeking behavior include socioeconomic status, stress levels, employment status, social support, and access to gender-specific (i.e., male-specific) health care services. There are also barriers at the level of health care providers. Nearly 67–90% of males with sexual dysfunction were not being assessed about their sexual dysfunction during physician visits. Most patients prefer their physicians to initiate discussion on their sexual health, rather than providing this information voluntarily. Variations in local customs, traditions, culture, beliefs, and health delivery systems can also contribute to these gaps in diagnosis and treatment. Health care providers also face several obstacles such as clinical inertia (lack of training), lack of time, patient’s discomfort or sexual health having lower medical importance than other conditions. They may assume that patients do not like to be asked about sexual problems, citing their concerns that the discussion may cause harm to the patient or be inappropriate for older patients. Some primary care providers think patients would be embarrassed talking about their sexual health unless they initiate it, as they worry that bringing up this issue without an apparent reason would lead to a patient’s suspicions of their intentions. Improved patient–provider communication plays a major role in long-term diabetes management. Due to social taboos, it may be prudent to choose a more sensitive screening method, such as self-administered questionnaires to reduce embarrassment. Patients prefer to discuss their sexual health with a primary care physician, gynecologist, and/or sex medical practitioner, especially in the presence of trusting patient–provider relationship. Hence, good continuity of care can lead to more opportunities and higher levels of comfort in discussing health issues. A more gender-specific approach to assess, stratify and improve men’s health should be integrated into routine diabetes care. Refusal of a diabetologist/endocrinologist to address the patient’s sexual health issues and referring them to a different specialty may result in diffusion and dilution of patient care. Hence, continuous training in sexual health among diabetologists, endocrinologists, and primary care physicians is required to provide holistic care. Integrating the service of allied health personnel such as nurses, diabetes educators, and pharmacists in the sexual health assessment can reduce the burden of physicians.
the majority of trained nurses and diabetes educators are females, which may pose a challenge for them to engage in an open and patient-centered discussion on sexual health. Nonetheless, there are studies suggesting that males might be more comfortable and assertive while speaking to female allied health personnel, especially when trust and rapport had been established.112,113

Traditional/complementary medicine plays a major role in Asian cultures. Studies have reported that Asian males tend to seek help from traditional complementary medical practitioners, especially for chronic illnesses, which were perceived as ‘controllable but uncurable’.96 Asians tend to believe strongly in traditional treatment which is said to ‘promote general well-being by restoring and realigning the body’s function’, with fewer side effects compared with Western medicine.114 Traditional/complementary medicine is often an alternative to avoid embarrassment with their health care providers, and to males who are worried about adverse effects of medications, or unhappy with the treatment provided.114 In Malaysia, 65% of males believed that traditional/complementary medicine was superior to Western medicine.115 However, more research is required to determine the efficacy and safety of traditional/complementary medicine.114,116,117

Approach to the management of sexual dysfunction in patients with diabetes

All males with diabetes should be routinely screened for sexual dysfunction as part of cardiovascular risk assessment during physician visits. Validated and self-administered questionnaires such as the International Index of Erectile Function (IIEF), can be used to assess sexual health while patients are waiting for consultation to avoid embarrassment and to overcome time constraints.118 Once diagnosed, males with erectile dysfunction should be assessed thoroughly for subclinical cardiovascular diseases.119 There is controversy on the routine testing of total testosterone levels in males with diabetes. To date, it is not recommended by professional organizations unless the patient has specific symptoms of hypogonadism.120,121 As obesity and insulin resistance reduce sex hormone-binding globulin (SHBG) levels, a free or bioavailable testosterone level should be used in patients with obesity and borderline low total testosterone levels.120 Males with established hypogonadism should be referred to an endocrinologist to investigate if it is primary or secondary hypogonadism.120

Lifestyle intervention, especially weight loss of at least 10% by any means, improves total and free testosterone levels.122-124 Very low-calorie diets (VLCD) or low-calorie diets (LCD) with physical activity could reduce insulin resistance and leptin levels with improvements in SHBG and total testosterone levels.125 A trial comparing the effects of LCD on insulin sensitivity, testosterone levels, and erectile function over 8-weeks in obese males who achieved a weight reduction (≥10% or more) found a significant increase in insulin sensitivity, testosterone levels ($r = -0.34$), and erectile function ($r = -0.26$), irrespective of their status of diabetes.126 A study on 104 randomly assigned men were given comprehensive instruction about lifestyle interventions such as weight reduction, increased physical activity, and choice of food reported that 23 males had their erectile function restored after 2 years.127 Similarly, in a randomized clinical trial which involved males with BMI $\geq 30$ kg/m² and hypogonadism, all were included in an intensive weight loss program comprising 10 weeks of hypocaloric diet, followed by 46 weeks of weight maintenance. Compared with those without testosterone replacement, males who received testosterone replacement had greater reductions in fat mass (mean adjusted-group difference [MAD] $-2.9$ kg, 95% CI $-5.7$ to $-0.2$) and visceral fat area (MAD $-2,678$ mm², 95% CI $-5,180$ to $-176$)128,129. Another clinical trial of 65 males from Australia with metabolic syndrome and erectile dysfunction, where one group was given instruction about the Mediterranean diet (comprising whole grain, seafood, fruits, vegetables, beans, and nuts). Two years later, 13/35 following the Mediterranean diet had a restoration of normal erectile function compared with the group who was only given general information on healthy food.130 Moreover, a prospective study in Singapore on meal replacements reported them as an effective strategy in reducing weight ($4.2 \pm 0.8$ vs $2.5 \pm 0.4$), abdominal obesity ($4.6 \pm 0.7$ vs $2.6 \pm 0.5$), and improving erectile function (IIEF scores: $3.4 \pm 0.7$ vs $2.5 \pm 0.5$) compared with a conventional reduced fat diet.131

The effects of testosterone replacement therapy in males with pre-diabetes or diabetes are debatable. Earlier studies reported that testosterone replacement therapy was associated with increased lean mass and reduced fat mass. Yet, the effects of testosterone replacement on insulin resistance and glycemic control are inconsistent.50 Previous trials have reported conflicting results on the effects of testosterone replacement therapy on quality of life, sexual function,132-136 glycemic control,124,133,134,137-141 and/or cardiovascular outcomes.142,143 A meta-analysis of eight trials of testosterone replacement therapy in males with type 2 diabetes and hypogonadism reported significant improvements in HOMA-IR (mean difference [MD] $-0.79$, 95% CI $-1.23$ to $-0.34$) and HbA1c (MD $-0.45\%$, 95% CI $-0.73$ to $-0.16$), but not for body fat percentage (MD $-0.33$, 95% CI $-0.92$ to $0.26$) and BMI (MD $0.29$, 95% CI $-0.84$ to $1.41$).144 Hence, professional organizations do not recommend testosterone replacement therapy in asymptomatic males with type 2 diabetes to improve their metabolic profiles.120,145

In the large-scale Testosterone for Diabetes Mellitus (T4DM) trial involving 1,007 obese males (waist circumference $>95$ cm and total testosterone $<14$ nmol/L), testosterone replacement therapy for 2 years was associated with a 41% reduced risk of progression to type 2 diabetes (relative risk [RR] 0.59, 95% CI $0.43$–$0.80$), mainly due to reduction in abdominal fat mass by 2.3% and increased total muscle mass by 1.7 kg.146 This finding resonated with another prospective study involving testosterone replacement therapy in 316 males with prediabetes and symptomatic hypogonadism (total testosterone $\leq12.1$ nmol/L). A
total of 90% of the treatment group had a HbA1c reduction of 0.39% and achieved normal HbA1c of <5.7%, compared with the untreated group.147

Treatment for erectile dysfunction and/or premature ejaculation can be initiated, regardless of the gonadal status (Figure 2). Apart from lifestyle interventions including weight loss, smoking cessation and increased physical activity level, phosphodiesterase type 5 inhibitors (PDE5 inhibitors) are currently recommended as the first-line treatment for erectile dysfunction in males with diabetes.148,149 PDE5 inhibitors can improve erectile function and quality of life, showing a higher efficacy with scheduled daily therapy vs an on-demand regimen.55,149 Notably, they are contraindicated in males with either untreated coronary artery disease or the concomitant usage of nitrates. Patients who are not responding to or contraindicated for PDE5 inhibitors should be referred to a urologist for second-line treatment such as vacuum constriction devices, intracorporeal/intraurethral prostaglandin E1 therapy, prostaglandin E1-papaverine-phenolamine combination therapy, or even penile prosthesis insertion (Table 1).55,149-151

Figure 2 | Proposed approach to addressing males health in a routine outpatient setting. IIEF, International Index of Erectile Function.
As serotonin is the primary neurotransmitter involved in the control of ejaculation, selective serotonin re-uptake inhibitors (SSRIs) such as dapoxetine are the mainstay of treatment for premature ejaculation. Besides, psychosexual-behavioral therapy can be used to identify psychological factors that may contribute to premature ejaculation, in which tailored management can be offered.

**CONCLUSION**

Sexual dysfunction, an early harbinger of cardiovascular diseases, is common in males with prediabetes and diabetes. However, addressing sexual health in Asian males has been challenging with multiple barriers at the levels of patients and health care providers. Assessment of sexual health with effective patient–provider communication should be integrated into routine practice to narrow the gaps in the management of males with prediabetes and diabetes.

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The authors declare no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Summary of previous literature on the prevalence of erectile dysfunction among patients with prediabetes

**Table S2** | Summary of previous literature on the prevalence of erectile dysfunction among patients with type 1 diabetes

**Table S3** | Summary of previous literature on the prevalence of erectile dysfunction among patients with type 2 diabetes

**Table S4** | Summary of previous literature on the prevalence of erectile dysfunction among patients with undefined type of diabetes