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Sexual Dysfunction in Asian Males with Type 2 Diabetes Mellitus

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Abstract: In 2021, 537 million people were diagnosed with diabetes globally, where over 90% of these cases were type 2 diabetes mellitus (T2DM). In the top 10 countries for many adults with diabetes in 2021, Asia accounted for six spots in the rankings, with China (140.9 million), India (74.2 million), and Pakistan (33 million) sitting at the top three. In addition, the prevalence of diabetes in Asians are higher than in individuals from other regions. In Asia, diabetes affects a younger age group resulting in more people suffering from the complications of diabetes at an earlier stage in life. One of the most serious diabetes mellitus (DM) complications is sexual dysfunction (SD). In men with diabetes, several issues may occur in SD, such as erectile dysfunction (ED), ejaculatory disorders, orgasmic disorders, and reduced libido. There are many tools available to assess SDs. However, the Sexual Dysfunction in Asian Men with Diabetes (SAD-MEN) questionnaire is the only tool specific to Asian males with diabetes. SD develops because of the interaction between several biopsychosocial factors. There is insufficient data on the genetic, psychological, and social factors contributing to SDs in males with diabetes in Asia. Men with diabetes induced SDs experience a poor quality of life (QoL) due to the distress caused by SD. However, people from different cultural backgrounds and ethnicities perceive QoL differently. Therefore, future studies must be done on other predictors of life in a multiethnic population like Southeast Asians. There is still insufficient data on SDs in Asian males with diabetes. More studies are warranted to research different aspects of SDs, such as its prevalence in other parts of Asia, biopsychosocial factors contributing to SD, and the impact of SD on the quality of life of males with diabetes.

Keywords: sexual dysfunction; type 2 diabetes mellitus; males; gene; quality of life

1. Introduction

Diabetes is a chronic health condition that affects the ability of the pancreas to produce sufficient insulin or when the produced insulin is not utilized effectively to digest glucose in the body for energy production[1]. Approximately 537 million people worldwide are currently living with diabetes, which is a 400% increase from 108 million in 1980[2,3]. According to the International Diabetic Federation (IDF), these values are predicted to reach a staggering number of 592 million by 2035[3]. Over 90% of diabetes is attributed to type 2 diabetes mellitus (T2DM), and this chronic condition has been dubbed the ninth leading cause of death as it claimed 1.5 million lives in 2019[2]. The 20-year prospective cohort study done by Iris Shai et al. (2006) showed that the Asian population is at a significantly higher risk (adjusted RR =1.43, 95% CI 1.08–1.90) of T2DM than Caucasians, contributing to 60% of DM cases worldwide[4,5]. This can be attributed to the increased susceptibility to insulin resistance due to the higher percentage of body fat in Asians compared to Europeans of the same BMI values[6]. Besides, a drastic increase in diabetic patients was also seen in the Asian population.

In the past 30 years, countries like Korea, Indonesia, and Thailand have experienced a three to five-fold rise in the number of people suffering from this chronic disease. There was a three-fold rise in diabetic patients in an even shorter time in China. Although there are an increase T2DM patients in other parts of the world, the changes were not as drastic as in Asia[6]. The prevalence is higher in this region; people from a younger age group are affected by this condition. Most people with T2DM in Asia are from 45 to 64 years old compared to Europeans who predominantly develop T2DM at the age of 65 and above[6]. Soon, more younger people in Asia will suffer from microvascular (e.g. retinopathy, neuropathy and nephropathy) and macrovascular (e.g. peripheral vascular, cardiovascular and cerebrovascular diseases) complications of T2DM[7]. Therefore, this review aims to discuss on the sexual dysfunction among men with type 2 diabetes mellitus (T2DM).

2. Sexual Dysfunction, a Serious Complication of T2DM

According to the World Health Organization (WHO), sexual dysfunction is described as the inability of a man or woman to have a sexually satisfying relationship with his or her partner[8]. In male diabetics, several issues may occur in the realm of SD. Other than erectile dysfunction (ED), which has been extensively researched for the past decade, male diabetics also suffer from ejaculatory disorders, orgasmic disorders, and reduced libido, which can be equally if not more distressing to diabetic men[8–10]. Not only is it distressing, but it also affects the fertility of these men[11]. Men with diabetes mellitus **(**DM) were at a higher risk of suffering from SD than non-diabetic men[9]. Thus, the primary focus of this paper will be on all SDs experienced by men with T2DM. The different SDs discussed in this paper are erectile dysfunction, ejaculatory disorders, orgasmic disorders, and reduced libido.

2.1. Erectile Dysfunction

Erectile dysfunction occurs when men frequently experience difficulty maintaining a penile erection during sexual intercourse leading to a dissatisfactory sexual experience[10]. In

diabetic males, the amalgamation of autonomic neuropathy decreased vascular nitric oxide levels, accelerated atherosclerosis, and increased oxidative stress due to endothelial dysfunction results in the development of ED[10,12]. This multistep mechanism makes diabetic men more vulnerable to ED than non-diabetic men[13]. It is still uncertain if hypogonadotropic hypogonadism, a common occurrence in diabetic men, contributes to ED[14,15]. Current evidence shows a wide range of prevalence for diabetes-induced ED in different parts of the world (35 to 90%)[8,16]. Asian countries have reported a higher incidence of ED compared to non-Asian countries. Sri Lanka, China, and Japan have documented a prevalence of 73.1%, 75.2%, and 80.9%, respectively, in contrast to the US and Italy which reported a lower prevalence of ED (45.8% and 43.3% respectively)[17–21]. Apart from Western countries, even in the African countries, diabetic men did not experience ED as frequently as the Asians[22]. Some of the results of studies on the prevalence of ED among diabetic men may be skewed for several reasons. The inclusion of many older men compared to younger participants will explicitly increase the overall prevalence of ED as the development of ED is shown to increase with age[13,20]. Furthermore, some studies did not exclude participants who have type 1 diabetes mellitus, leading to inaccurate results as this group of men may experience ED as well[17,23].

In Southeast Asia, there is still a lack of high-quality, large-scale studies done on the prevalence of ED among diabetic males. A cross-sectional study showed that 84.4% of Indonesian diabetic men had ED. However, the sample size is too small to make a definite conclusion on the prevalence of ED[24]. Malaysia has reported a 70.1% prevalence rate of ED among men aged 50 to 93 but did not stratify participants between diabetic and non-diabetics[25]. The prevalence of ED is predicted to increase drastically in all regions worldwide, especially in Asia[17]. This can be attributed to the high prevalence of ED, as shown by the studies done in this region. However, the results of these studies do not reflect accurately on the prevalence of diabetes induced-ED in SA as this region is more diverse in terms of ethnicity[8]. In the general population, the prevalence of ED in SA is higher than in other parts of Asia, warranting more research to determine the percentage of them experiencing ED due to T2DM[26].

2.2. Ejaculatory Disorders

Ejaculatory disorders in diabetic men include premature ejaculation (PE), delayed ejaculation, anejaculation, and retrograde ejaculation. PE can be categorized into acquired premature ejaculation and lifelong premature ejaculation[27]. Acquired PE is defined as ejaculation, which always or almost always occurs within three minutes of penetration and frequently struggles to delay ejaculation upon vaginal penetration. It is also associated with extreme distress and exasperation, resulting in the affected men being sexually intimate with their partners[10,27]. In comparison, delayed ejaculation is the complete absence of a delay in reaching orgasm after usual sexual excitement during sexual intercourse. It is often associated with extreme distress in the patient[10]. Another form of the ejaculatory disorder is anejaculation which is the absence of ejaculation with or without an orgasm. Lastly, retrograde ejaculation describes the retrograde movement of semen into the urinary bladder

due to the disruption in coordination between the internal urinary sphincter and external urinary sphincter during ejaculation[10,28]. Retrograde ejaculation can either be partial or complete, leading to infertility[10,29].

It is vital to address ejaculatory disorders in T2DM patients due to their higher prevalence in diabetic males than in general. A cross-sectional study conducted in Sri Lanka and Egypt showed that 40.2% of diabetic men had PE whereas, in Italy, the prevalence rate was 28.3%[8,21,30,31]. In Malaysia, a high prevalence rate was shown in both Malay and English speaking participants (38% and 46% respectively)[8]. The studies were done in Sri Lanka, Malaysia, and Italy did not exclude participants who had lifelong PE, which may have contributed to a higher prevalence rate of PE. Unlike ED, age is not a risk factor of PE[27]. Data on the other ejaculatory disorders listed above are still scarce, as there are very few studies on these conditions. However, a small-scaled study done in Denmark showed 34.6% of diabetic men had retrograde ejaculation[29]. Small sample size is a limitation to this study, warranting more studies to be done on retrograde ejaculation. As of now, there is also no definite normal range to the number of spermatozoa that can be present in post-ejaculation urine, making the diagnosis of retrograde ejaculation inconsistent. Ejaculatory disorders in diabetic males are still a poorly researched topic around the world. Besides the study done in Malaysia and Sri Lanka, there are no other studies conducted in the multiethnic groups that exist in the SA.

2.3. Other Sexual Dysfunctions

Orgasmic disorders can manifest as the inability of having an orgasm, delay in reaching orgasm, and reduced intensity of orgasm[10]. The results of a large-scale cross-sectional study done in the US found no significant difference between the prevalence of orgasmic disorders in men with and without diabetes[32]. Without other studies about this disorder, it is impossible to determine the risk of orgasmic disorders in men with T2DM.

In addition, men with T2DM can also experience reduced libido, resulting in a significant reduction in sexual fantasies and sexual desire. Reduced libido in diabetic men may be caused by hypogonadism[10]. In the aforementioned study, men living with DM had a significantly higher risk of experiencing reduced libido (AOR = 1.72, 95% CI 1.12–2.63)[32]. In the Asian population such as Sri Lanka, a 25.3% prevalence rate was reported among diabetic men[18]. Over the years, very few studies have been conducted on decreased libido in diabetic men. One of the community-based studies on non-diabetic men showed not only did more Japanese men experience reduced libido compared to Americans, but libido was also found to decrease with age[33]. Since T2DM increases with age, it is of utmost importance to investigate the relationship between T2DM and reduced libido in different populations.

2.4. Coexisting SDs

Different SDs have been seen to coexist in patients with T2DM. For instance, PE is said to exist concomitantly with ED due to the development of performance anxiety that arises from ED. Diabetic men with ED rush through their sexual intercourse, leading to faster

ejaculation[31]. In the cross-sectional study done by Malavige *et al*., ED was significantly associated with both PE (OR = 4.41, 95% CI 2.08–9.39) and reduced libido (OR = 4.38, 95% CI 1.39–13.82). On top of that, the prevalence of PE was also found to increase as the severity of ED increases[30]. However, this study did not stratify males who had lifelong PE and acquired PE, which is a significant downside of this study. Another study in Egypt also showed a strong link between PE and ED[31]. Future studies must explore different types of SDs that may coexist in a diabetic male, as there is evidence of it occurring in other populations in the world.

2.5. Diagnosing Sexual Dysfunctions in Asian Men with Diabetes

The diagnosis of SD should be made by taking a complete medical history, including the sexual history, examining the patient for other T2DM complications, and screening for androgen deficiency[10]. Validated questionnaires play a pivotal role in assessing SDs in patients because sexuality and sexual functioning are sensitive topics to discuss, even with doctors. Therefore, self-administered questionnaires ease the history-taking process by allowing patients to self-report SDs on paper and overcome barriers that may prevent them from being frank about their condition. The International Index of Erectile Dysfunction (IIEF) is an internationally validated diagnostic tool used to assess the sexual functioning of men across five domains which are erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Nevertheless, IIEF should not be used as a primary measure for PE and reduced libido as it is only validated for ED[34]. The International Index of Erectile Function-5 (IIEF-5) is a five-item questionnaire that is a simplified version of IIEF to assess ED. This highly sensitive and specific diagnostic tool includes four items from the erectile function domain and one from the intercourse satisfaction domain from IIEF[35]. This questionnaire has been used in many studies to assess ED in diabetic men, although it is not specific for diabetes-induced ED.

The validated tools available for use in PE are Premature Ejaculation Profile (PEP), Index of Premature Ejaculation (IPE), and the Premature Ejaculation Diagnostic Tool (PEDT). However, the PEP and IPE do not have validated cut-off scores to diagnose PE, and all of the tools are not specific for their use in the Asian population[36]. A newly available tool called the SAD-MEN questionnaire can assess SD among Asian men with DM. This questionnaire consists of three parts; the first part assesses the individual's demographics, medical background, medications, and social history. The second part involves examining the history of existing sexual dysfunctions, while the last part includes inquiries about the sexual functioning of the individual. Questions assessing sexual functioning were divided into two components which are sexual performance and sexual desire, both of which have Cronbach's α values of 0.949 and 0.775, respectively, indicating high internal consistency. SAD-MEN also considers other factors contributing to SD other than T2DM, such as polypharmacy and side effects of medications. Unlike the IIEF-5, this questionnaire can be used for ED, PE, and reduced libido[8]. Therefore, the SAD-MEN questionnaire is a stepping stone to conducting more studies on SD in diabetic men residing in Asia, especially Southeast Asia.

3. Modifiable and Non-Modifiable Risk Factors of Sexual Dysfunction

To determine the susceptibility of men with DM to SD compared to men with other types of diabetes, studies have been extensively done across patients with different demographics and varying medical histories. Studies have also been done to investigate the risk factors contributing to the development of diabetes-induced SD (Table 1).

T**able 1.** Current evidence of precipitating factors of sexual dysfunction.

Type of study	Reference	Results
Meta-analysis	[37]	• There is a significant association between depression and ED in diabetic men
Systematic review	[10]	• Factors influencing the development of ED include duration of DM, age, blood glucose levels, smoking, hypertension, dyslipidemia, obesity, lack of physical activity, other DM complications, medications (eg. antidepressants, beta-blockers, thiazide, spironolactone, fibrates), and other medical conditions (hypogonadism, mood disorders such as depression, Peyronie's disease) • Factors influencing the development of PE include longer duration of DM, poor control of blood glucose level, coexisting ED, and other complications of DM • Reduced libido is associated with older men, coexisting ED, other comorbidities (eg. depression, hypogonadism, cardiovascular disease, kidney failure), and medications (eg. antidepressants, antihypertensives)
Prospective cohort	[31]	• The prevalence of PE doubled in diabetic men 50 years old and above compared to men younger than 50 • Men with DM for more than 10 years, poor metabolic control, coexisting cardiovascular disease are at a higher risk of PE

Cross-sectional	[38]	• Significantly increased risk of ED in men who have diabetes for more than five years, hypertensive, consumes more than two standard drinks of alcohol daily, BMI > 25 kg/m2, beta-blockers, and other microvascular complications of T2DM • No significant associations to household income, education, dyslipidemia, macrovascular complications of T2DM, good control of blood glucose levels (HbA1c < 7) and smoking
Cross-sectional	[9]	• No significant difference in the prevalence of ED among South Asian men with DM as compared to the Europeans
Cross-sectional	[22]	• Age more than 41, uneducated, divorced or widowed, DM comorbidities (nephropathy, retinopathy, diabetic neuropathy, diabetic foot ulcer, cardiovascular diseases, hypertension), practicing sedentary lifestyle, and depression were significantly associated with SD in men with DM • No significant associations were found between SD and sex, religion (Orthodox, Protestant, Muslim, others), ethnicity, and duration of treatment for DM
Cross-sectional	[39]	• The risk of ED is shown to increase in older men, living with extended family, high BMI, on combined treatment for DM, presence of other complications of DM, smoking, depression, poor marital relationship
Observational study	[21]	• The risk of ED is significantly increased with severe depression, beta-blockers, and at least one complication of T2DM • PE was significantly associated with severe depression • Reduced libido was increased dramatically in men with severe depression, hyperprolactinemia, and obesity (BMI > 30 kg/m2). Consumption of coffee, however significantly decreased the risk of reduced libido

When it comes to the Southeast Asian population, there are still many unanswered questions regarding the risk factors of SD in diabetic men due to the lack of studies being done in these populations. Several studies done elsewhere have shown that the development of SD in men with T2DM is dependent on a range of biopsychosocial factors. Unfortunately, the results of these studies cannot be applied to the population in Southeast Asia due to the cultural and ethnic variation in this region. Moreover, due to the cross-sectional nature of most of the studies, a temporal causal-effect relationship between the independent factors and SD cannot be formed. For instance, in Asian diabetic men with depression and ED, did the depression precipitate ED, or is ED a manifestation of depression? The only way to answer this is to conduct more prospective studies to determine factors that influence the development of ED.

Future studies should investigate unexplored psychosocial factors affecting the development of SD in men with T2DM. Sexual behavior is influenced by the religion and religiosity of a person[40]. Thus, this factor can potentially play an important role in the development of SD among males in Southeast Asia, the home of a religiously diverse population. A study on Malaysians residing in urban areas showed a high prevalence of ED[25]. Future studies should be done on the rural population to make comparisons as the different lifestyles of both urban and rural people may influence the prevalence of SD. It is essential to identify all of the risk factors of ED in this population because most Asian men tend to attribute SD to aging and choose to suffer in silence[41]. Knowing all of the predisposing factors of SD in a diabetic man can help physicians predict its development in a patient.

4. Quality of Life of Diabetic Men with Sexual Dysfunction

Quality of Life (QoL) is defined as an individual's perception of their position in life regarding their culture, value systems, goals, expectations, standards, and concerns[42]. In the context of T2DM, measuring only the biological outcome of DM is insufficient as DM is a chronic disease that affects the biopsychosocial well-being of a person. Therefore, psychological and social factors affecting a person’s life should be considered to improve their QoL[43]. One of the predictors of QoL in diabetic men is SD as it is linked to the psychological derangement of these men. Men with ED develop low self-esteem due to their inability to perform sexually, which importantly translates into poor self-care resulting in poor glycemic control[9,44]. ED was also shown to be emotionally distressing, as illustrated in the cross-sectional study by Chen *et al*., using the Symptom Checklist 90-Revised (SCL-90-R) questionnaire[45]. However, that was the only study of its kind, warranting more studies to be conducted on the association between emotional distress and SD in different populations.

A large-scale prospective study done by Berardis *et al.* shows that the development of ED was significantly associated with the deterioration in the physical and mental well-being of these men, as measured by the 36-item short-form health survey (SF-36)[46]. The limitation of this study is the failure to use a validated questionnaire to diagnose ED. Another study has explored other SDs in diabetic men, such as PE and reduced libido, and found significant associations between these SDs and QoL. In this study, ED was significantly associated with poor QoL on both the physical and mental scales of SF-36 and reduced libido on the physical scale. The strength of this study is the usage of the disease-specific Psychological Impact of Erectile Dysfunction (PIED) questionnaire to measure the impact of ED on QoL. ED reduced libido and PE were significantly associated with poor quality of sexual experience, whereas poor emotional life was associated with ED and reduced libido[18]. A comprehensive study was conducted in Malaysia to evaluate different factors influencing QoL in men with T2DM using the disease-specific Asian Diabetes Quality of Life (AsianDQoL) questionnaire. This study also showed the significant association between SDs and QoL of English-speaking men from different ethnicities[47]. The aforementioned study represents how people from various cultural backgrounds have different perceptions of QoL. For instance, the QoL of English-speaking Chinese were only affected by SD compared to Mandarin-speaking Chinese men, who are concerned about hyperlipidemia and HbA1c levels in addition to SD. This differed from Malay and Indian men who had other predictors of QoL[47]. In the context of SDs, it is important to find the association between different ethnicities in SA and how SDs affect their QoL to provide more holistic management of T2DM.

5. Genetic Factors Associated with Sexual Dysfunction in T2DM

Several candidate genes are associated with the development of SD in males with T2DM. However, most animal and human studies conducted are much focused on ED in males with T2DM. One of the better-studied genes is the *eNOS* (endothelial nitric oxide synthase) gene. Chromosome 7q35 codes for the *eNOS* gene. The size of this gene is 21 kb, and it consists of 26 exons[48]. One of the eNOS gene variants is G894T[49]. The single-nucleotide polymorphism at position 298 in exon 7 led to the transversion of guanine with thymine, resulting in the substitution of glutamate with aspartate in the mature protein[49–52]. This polymorphism increases the selective proteolytic cleavage of endothelial cells and vascular tissue leading to the reduction in the NOS activity and subsequent decrease in the production of vascular NO. The 786T-C polymorphism gives rise to another variant of the *eNOS* gene. This variant inhibits the activity of the gene promoter. As a result, there was a reduction in the expression of *eNOS* protein, thus decreasing the activity of the protein[50,53].

A decrease in constitutive nitric oxide synthase (cNOS) expression is significantly associated with ED in males with DM. As shown by an animal study conducted by Ahn *et al*., a marked downregulation in the neuronal nitric oxide synthase (nNOS) and eNOS mRNA expression levels is seen in the corpus cavernosum tissue in rats induced with DM compared to controls[54].

A study conducted on 228 Taiwanese males showed a significantly increased risk of ED in *eNOS* 894T allele carriers compared to *eNOS* 894G allele carriers (80.0 % vs. 63.3 %; $p = 0.04$). This suggests the association of G894T polymorphism to ED in the general population[52]. However, a study conducted in Brazil showed that G894T polymorphism is not associated with ED development (OR = 1.05, 95% CI 0.69–1.60; $p = 0.86$)[55]. Another study on T-786C polymorphism in the promoter of the *eNOS* gene in the Turkish population showed a significant increase in the prevalence of ED in CC alleles carriers (OR = 3.2; 95% CI 1.4–7.6; $p = 0.006$). Males with CC genotype were shown to develop earlier symptoms of ED compared to controls (51.7% vs. 10.7%; $p < 0.001$). However, the small sample size is a limitation of this study[56]. In males with T2DM, evidence on the association between *eNOS* gene polymorphisms and the development and/or progression of vasculogenic ED is replete with conflicting results. A study conducted in Tunisia included 164 males with T2DM and 148 healthy males subjected to genotyping for *eNOS* gene polymorphism (G894T and T-786C). The result of this study shows that G894T (COR = 1.66, 95% CI = 1.16–2.38; $p = 0.005$) and T-786C (COR = 1.46, 95% CI = 1.05–2.04, p = 0.02) polymorphisms are significantly associated to vasculogenic ED among males with T2DM[53]. Another study conducted in Taiwan showed a higher prevalence of 894T allele carriers in males with DM than males without DM, although not statistically significant (32.5% vs 13%; $p = 0.13$)[52]. *eNOS* polymorphisms occur at a different frequency among various ethnic groups. These differences lead to a lack of reproducibility of results across different populations[48]. Furthermore, the lack of evidence on the variants of the *eNOS* gene concerning ED in males with T2DM makes it harder for a conclusion to be drawn.

Angiotensin-converting enzyme (*ACE*) is another gene commonly associated with ED. The ACE gene codes it, and it is responsible for converting angiotensin I (Ang I) to angiotensin II (Ang II)[48]. The insertion (I) or deletion (D) of a 287 bp region in the intron 16 of the *ACE* gene is responsible for the alteration of serum *ACE* levels[57]. These variants give three possible genotypes: DD, DI, or II[48]. The D allele increases ACE activity in the body[57]. In a study conducted by Mazo *et al*., DD alleles were significantly associated with ED development in Russian males with metabolic syndrome ($p < 0.001$). The author hypothesizes that the increase in the *ACE* activity leads to the dysfunction of the endothelial

cells, resulting in ED[58]. Another study performed on 84 Japanese males showed a significant relationship between the DD genotype and ED ($p < 0.01$)[59]. To date, there is still insufficient evidence to prove the association of the D allele and the development of ED in males with T2DM.

The peptide Ang II plays a role in balancing the cavernous smooth muscle tone by inducing contraction, initiating detumescence in males[60]. *Ang II* gene plays a key role in the mechanism of ED in males with DM. In an animal study conducted by Zhang *et al*., male Sprague-Dawley rats with DM and silenced *Ang II* gene demonstrated a significantly longer penile erection time (1.3 ± 0.6 min, $p < 0.05$) compared to rats in DM-induced ED and Ad-null groups. *Ang II* silencing was shown to inhibit the expression of the RhoA/Rho-kinase signaling pathway, thus decreasing contraction and increasing relaxation of smooth muscles to improve erectile function[61].

The extracellular matrix of erectile tissue encompasses collagen, elastic fibers, and different types of proteoglycans[62]. In males with DM, these intracavernous components (i.e., elastic fibers) are significantly reduced compared to healthy counterparts. This alteration results in the deterioration of erectile function[63,64]. Sullivan *et al*. demonstrated the downregulation of extracellular matrix genes (i.e., collagen and elastin) such as genes encoding collagen (i.e., type 1, 3, 5, 6, and 11), elastin, and fibrillin1 in DM[65]. Lysyl oxidase mitigates the stabilization and covalent crosslinking of collagen and elastin fibers in the extracellular matrix[66]. The gene expression that codes for lysyl oxidase, lox, is also reduced in the erectile tissue of males with DM[65].

Programmed cell death 4 (*PDCD4*) is a putative gene regulated by microRNA-21-5p, associated with ED in DM. The animal study by Huo *et al*. demonstrated the upregulation of the *PDCD4* in the cavernous tissue of rats with DM-induced ED. This leads to apoptosis and a decrease in the proliferation of smooth muscle cells of the corpus cavernosum[67]. Lipoprotein lipase (*LPL*) is another putative gene highly expressed in DM-induced ED. An in vitro study showed that the upregulation of long noncoding RNA myocardial infarction was associated with transcript (lncRNA-MIAT) in vascular smooth muscle cells of the corpus cavernosum combined with the downregulation microRNA-328a-5p (miR-328a-5p), upregulates the *LPL* gene. This concert of events leads to the injury of endothelial cells, ultimately causing the inhibition of eNOS[68].

Insulin-like growth factor-1 (*IGF-1*) plays a vital role in the regeneration of nerve fibres with the nNOS in dorsal and intracavernosal nerve[69]. In an animal study conducted by Pu *et al*., rats that were transfected with AdCMV-IGF-1 demonstrated a significantly higher ratio of maximal intracavernous pressure-to-mean arterial pressure (ICP/MAP) upon

cavernosal nerve stimulation compared to controls ($p < 0.05$). This proves the importance of the *IGF-1* gene in regulating penile erection[70]. More studies are required to highlight the relationship between genetic composition and ED in Asian males with T2DM. To date, there is still a lack of evidence on the association between genetic factors and other types of SD, such as ejaculatory disorders, orgasmic disorders, and reduced libido.

6. Conclusion

The existing evidence shows that SD is a severe complication of T2DM that is more prevalent among Asian men than men from other regions. As SD is one of the main predictors of QoL in Asian males with diabetes, efforts to improve their QoL should include the SAD-MEN questionnaire, a validated tool to assess SD. Moreover, there is a range of biopsychosocial factors influencing the development of SD; hence, identifying each patient's risk factors could greatly help physicians develop an effective treatment plan. However, more work on diabetes-induced SDs needs to be done in SA as there is still a lack of data of this issue in this region. Studies should explore more on SDs other than ED as they are proven to occur in males with diabetes. The prevalence and risk factors of orgasmic disorders, ejaculatory disorders, and reduced libido are still understudied, warranting more studies to be done in the future. We should also look into the psychosocial factors affecting the development of SDs among men with T2DM in SA. Future studies should focus on the degree of emotional distress caused by SDs and how the QoL of different populations with different cultural backgrounds, ethnicities, and religions are affected by SDs.

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