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Review

Type 2 diabetes mellitus: a silent threat to male and female infertility

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and hyperglycaemia, with global prevalence rising at an alarming rate. Beyond its well-established role in cardiovascular, renal, and neurological complications, T2DM exerts a significant yet often overlooked impact on reproductive health. This review synthesizes current evidence on the relationship between T2DM and infertility in both males and females, exploring epidemiological trends, molecular mechanisms, and clinical implications. T2DM contributes to infertility through endocrine dysfunction, oxidative stress, chronic inflammation, and microvascular damage, disrupting gonadal steroidogenesis, gametogenesis, and implantation. Genetic predisposition plays a critical role, with variants in genes such as *PPARG*, *IRS1*, *IRS2*, and *SHBG* influencing susceptibility and severity of reproductive impairment. Emerging data suggest that T2DM-induced reproductive dysfunction is mediated by a complex interplay of metabolic, hormonal, and genetic factors, underscoring the need for precision medicine approaches. Despite growing research, significant gaps remain, including a lack of longitudinal studies, underrepresentation of male infertility data, and limited exploration of epigenetic mechanisms. Addressing these gaps through multidisciplinary, multi-omics, and intervention-based studies could improve fertility outcomes in individuals with T2DM.

Keywords: type 2 diabetes mellitus, Infertility, Reproductive dysfunction, Genetic polymorphisms

Introduction

Infertility is characterized as the inability to conceive after having a consistent, unprotected sexual intercourse for one year or more [1]. Approximately 186 million people globally are impacted by infertility [2]. About 17% of individuals will experience infertility at some point in their lives, and prevalence rates are constant across countries regardless of income levels. Infertility affects 17.8% of individuals in high-income countries and 16.5% of individuals in low- or middle-income countries, respectively [3]. Infertility can be caused by both male and female factors [4]. Female infertility is frequently caused by uterine problems, menstrual and ovulation issues [5]. It is recognized that male infertility causes a decrease in the production of sperm with increasing motility and normal morphology [6].

According to recent studies, Diabetes has been linked to both male and female reproductive dysfunction [7]. Globally, Type 2 Diabetes Mellitus (T2DM) is becoming a more frequent health issue that impacts people of all income levels and places a significant strain on healthcare systems [8]. T2DM distresses an estimated 462 million persons globally or 6.28% of the overall population [9]. The progression of Type 2 diabetes is one of the most predominant metabolic diseases in the world, which is mostly brought on by a combination of two major factors which including the pancreatic beta cells' impaired ability to secrete insulin and the tissues' incapacity to react with insulin [10]. T2DM typically impacts male reproductive function on several levels, such as ejaculation, erectile dysfunction, and structural alterations in reproductive organs [11]. Women with type 2 diabetes may have a shorter reproductive

period as a result of delayed menarche and premature menopause. They also face a higher risk of infertility and irregular menstrual cycles [12]. The occurrence of T2DM is influenced by the intricate interaction of metabolic, genetic, and environmental susceptibilities [13]. T2DM risk is significantly influenced by genetic predisposition. Numerous genome-wide association studies of T2DM have demonstrated the complicated polygenic character of the disease during the past ten years [14, 15].

Several genes, including Peroxisome proliferator-activated receptor gamma (PPARG), Insulin receptor substrate 1 and 2 (*IRS1 and 2*), and Sex Hormone-Binding Globulin (*SHBG*) have been identified as increasing the risk of causing Type 2 diabetes [16].

These genes also play a role in infertility through pathways involving hormone imbalance, insulin resistance, and defective gametogenesis etc. This review purposes to examine the effects of Type 2 diabetes on the reproductive health of both men and women in the context of growing evidence that the disease raises the risk of infertility. It explores the mechanism linking T2DM and infertility, the impact of male and female infertility with type 2 diabetes, and the molecular and genetic underpinnings. It also talks about clinical implications, approaches to management, and identifies research gaps to help improve the inhibition and treatment of infertility linked to type II diabetes.

Overview of T2DM

Approximately 95% of the 537 million people with diabetes worldwide between the ages of 20 and 79 who had the disease as of 2021 were T2DM cases [17]. By 2045, this amount is anticipated to rise by 46% to 783 million [18]. India has the second-highest number of T2DM sufferers worldwide after China [19].

Pathophysiology of T2DM: beta cell dysfunction and insulin resistance

The pancreas (β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue are among the organs implicated in the progression of type 2 diabetes [20]. Diabetes type 2 is primarily caused by beta cell failure, which is exacerbated by insulin resistance (IR). IR and beta cell dysfunction continue to have a very complicated relationship. Both can be brought on by the beginning of hyperglycemia. Compared to IR, beta cell malfunction is more severe. Insulin secretion is compromised in beta cell failure, while IR may result in insulin secretion, but insulin sensitivity shows as a target problem. As IR and beta cell dysfunction worsen, hyperglycemia increases and type 2 diabetes develops (Figure 1) [21]. Even when there is high insulin levels present, a defective response to insulin by adipose tissue can lead to elevated release of free fatty acids (FFA) into the plasma, impaired glucose uptake, and poor suppression of lipolysis [22]. FFA buildup in the liver can also result in reduced glucose-stimulated insulin response and hepatic gluconeogenesis by impairing insulin signaling, which can cause type 2 diabetes [23]. The main features of patients with T2DM are obesity or an increased percentage of fat in the body, which is mainly found in the abdomen [24]. Emerging evidence points to the involvement of immunological dysregulation, inflammation, and anomalies in gut microbiota, as well as adipokine imbalance have become significant pathophysiological elements [25].

Role of obesity, metabolic syndrome, and inflammation

T2DM and obesity are closely related conditions that are becoming more prevalent globally [26]. 90% of persons with type 2 diabetes are obese, making obesity a key modifiable risk factor for the onset of the disease [27]. Obesity is characterized by an excessive buildup of adipose tissue to the point where it compromises one's physical and mental health [28]. Excess glucose and insulin are the fundamental causes of obesity. Adipocytes store excess glucose as triglycerides or "fat" when the body has more of it than is needed for the heart, skeletal muscle, and physiological processes [29]. Obesity is a major aspect in the expansion and progression of metabolism-related T2DM, which has a predictable outcome where hyperglycemia is brought on by decreased insulin sensitivity as a result of decreased functional beta-cell mass. However, a gradual increase in body weight is the catalyst for the development of future metabolic illnesses, the most closely associated of which is undoubtedly type 2 diabetes [30].

Globally, metabolic syndrome has become an epidemic, presenting a serious public health concern [31]. The metabolic syndrome (MetSy) is characterized by central obesity, high triglycerides, low high-density lipoproteins, hyperinsulinemia, hypertension, and glucose intolerance [32]. The definition, ethnic background, age, gender, and lifestyle of the study group are some of the variables that affect the prevalence of MetSy. Worldwide, the number of cases is rising quickly.

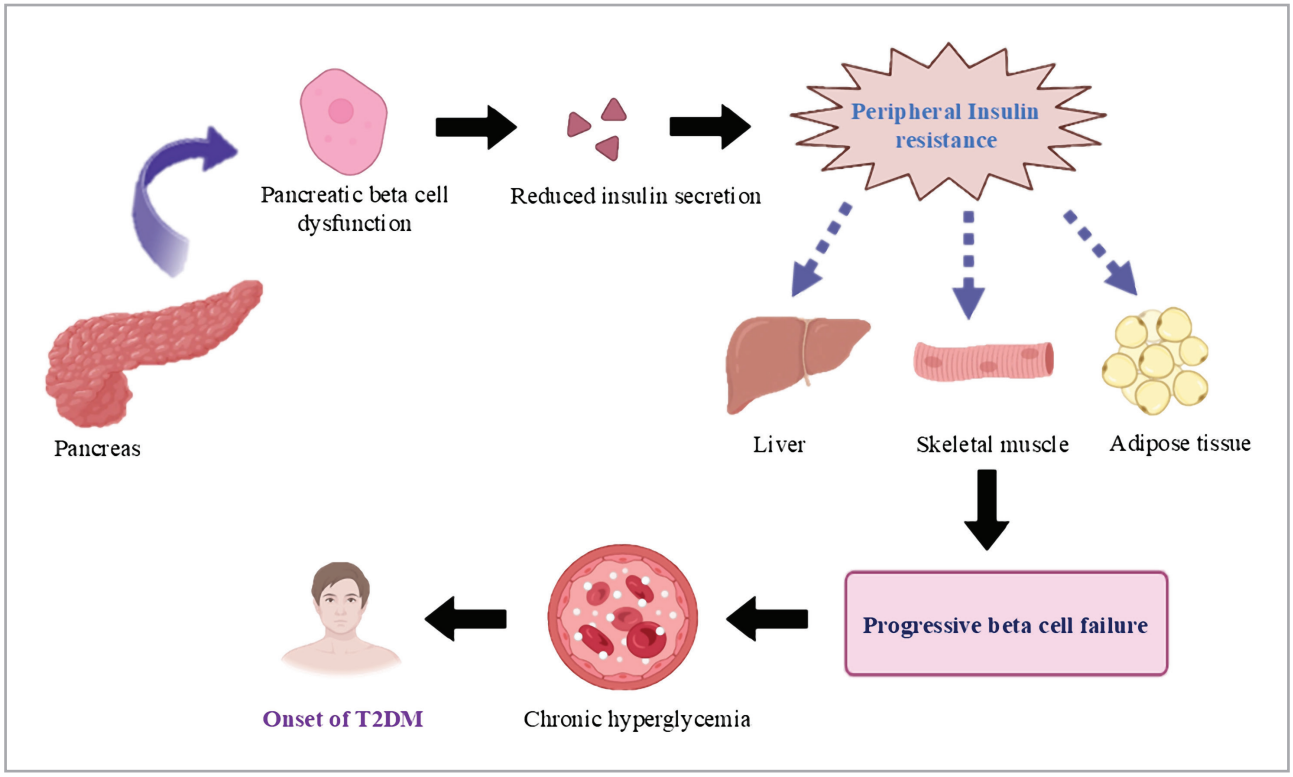

Figure 1: Pathophysiology of T2DM.

This has been attributed to alterations in dietary habits, physical inactivity, and sedentary behaviours [33]. T2DM risk is greatly increased by metabolic syndrome via a number of important pathways. The metabolic syndrome's defining feature, insulin resistance, causes increased insulin production by pancreatic beta cells and decreased glucose tolerance. Beta cell failure may eventually develop from long-term hyperinsulinemia and insulin resistance, maybe as a result of lipid and glucose toxicity, leading to type 2 diabetes [34].

The body uses inflammation as a physiological reaction to a number of pathological events, including tissue damage, pathogen invasion, and irritants [35]. An inflammatory reaction is triggered by certain proinflammatory cytokines. Proinflammatory cytokines induce mitochondrial stress and other reactions, which result in beta cell death [36]. The forthcoming prevalence of type II diabetes in adults was predicted by the presence of inflammatory mediators, according to an early study by Schmidt *et al.* [37]. It is unclear how chronic inflammation leads to the progression of T2DM, but it has been noted that adipose tissue can synthesize the key pro-inflammatory cytokines tumour necrosis factor and interleukin-1 and -6, and that inflammatory biomarkers are associated with body fat mass. These findings imply that inflammation and activated innate immunity play a significant biological role in the pathophysiology of DM as well as in the sequelae of type 2 diabetes [38].

Mechanism linking T2DM and infertility

The link between T2DM and infertility is caused by a number of interconnected pathophysiological processes. These consist of hyperglycemia and oxidative stress, IR, chronic inflammation and cytokine imbalance, and endothelial dysfunction. Together, these disruptions affect the hormonal axis and overall reproductive capacity. To give a thorough grasp of how type 2 diabetes impacts both male and female fertility, the ensuing section examines these methods (Figure 2).

Hyperglycemia and oxidative stress

Chronic hyperglycemia can lead to glucotoxicity, which accelerates the onset and progression of type 2 diabetes [39]. Excessive AGE production, elevated oxidative stress, and hyperglycemia are all correlated in the early stages of type 2 diabetes [40]. The generation of reactive oxygen species (ROS) by a particular cell, tissue, or fluid beyond the protective potential of the inherent antioxidant processes results in oxidative stress. This condition could cause sperm DNA

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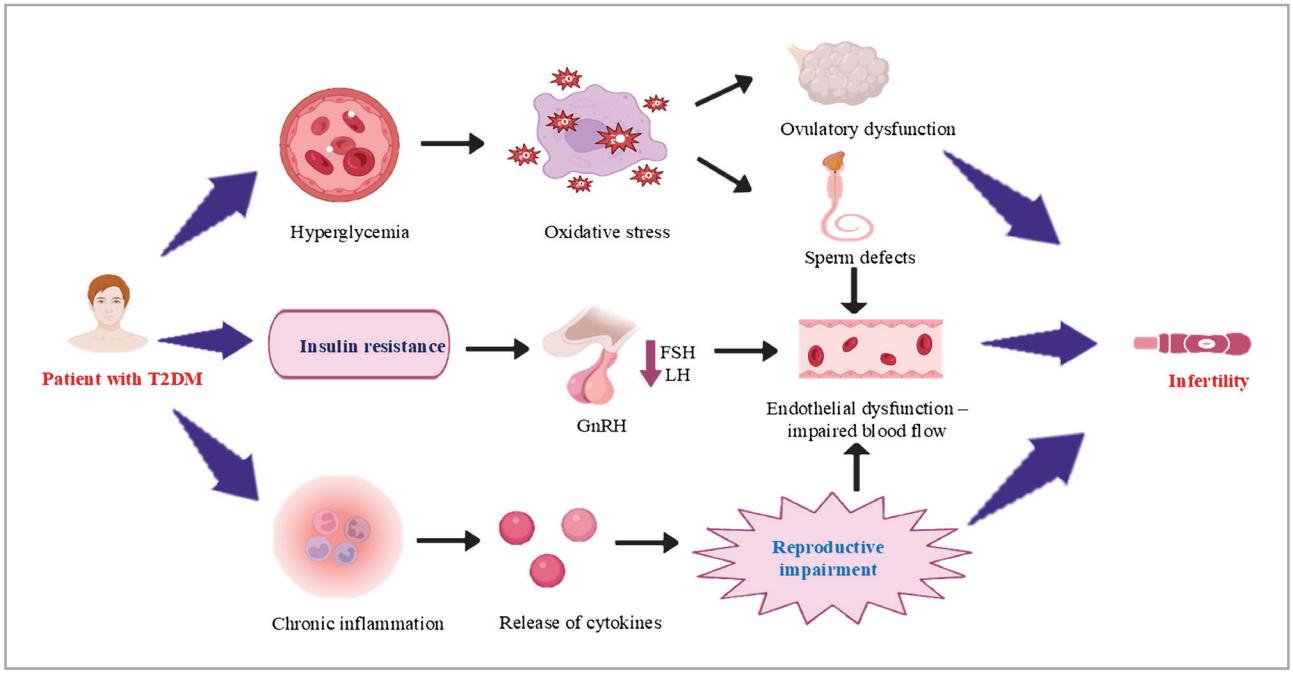

Figure 2: Mechanistic Links Between T2DM and Infertility.

fragmentation, sperm defects, spermatozoa damage, and potential cases of varicocele and testicular torsion in men. On the other hand, it may cause endometriosis, premature ovarian failure, and polycystic ovarian syndrome (PCOS) in women [41].

Insulin resistance and hormonal imbalance

An inability of the blood's insulin to adequately promote glucose absorption and utilization by insulin-sensitive organs and tissues is known as IR. When blood glucose levels rise in a healthy body, pancreatic beta cells react by generating insulin and preventing the liver from making glucose. When there is insulin resistance, the body produces more insulin in the pancreas and glucose in the liver because not all signals are correctly read [42]. Obesity and metabolic syndrome are frequently linked to insulin resistance in men. In addition to lower levels of general health, these disorders are linked to a decline in fertility. Not much research has been done on the effect of IR on male fertility in particular. However, there are indirect correlations that indicate it influences men's sex hormone levels and semen quality [43]. PCOS is the condition that has drawn the greatest clinical attention in women with IR [44].

Chronic inflammation and cytokines

Depending on the infection and immune response, the inflammatory response produces a variety of cytokines, chemokines, and adhesion molecules. Multiple signaling pathways are triggered when PAMPs and DAMPs activate Toll-like receptors (TLRs). This leads to the release of chemokines like CXCL8 and CXCL10 as well as pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α. These elements can harm male reproductive health by focusing on Leydig cells, which produce testosterone, and Sertoli cells, which are essential for spermatogenesis [45]. There is growing interest in the precise effects of chronic inflammation on female fertility, in addition to its implications on general human health issues. Several reproductive illnesses, including primary ovarian insufficiency (POI) and PCOS, have been linked to chronic inflammation [46].

Endothelial dysfunction and vascular effects

The biochemical characteristics of the vascular wall are changed by endothelial dysfunction, oxidative stress, platelet hyperreactivity, and inflammation as a result of this imbalance being disrupted in type 2 diabetes [47]. Endothelium dysfunction, which manifests as a diminished ability of the vessels to react to chemical and physical stimuli, can be assessed using a number of direct and indirect criteria that are intended to identify the primary endothelium mediator [48]. The endothelium is a monolayer of cells that lines the inside of all blood arteries. It has protective qualities that are necessary to preserve physiological vascular functioning when vasoconstriction and vasodilation stimuli are

balanced. In order to maintain the homeostasis of the reproductive system, endothelial cell activity is directly linked to the action of sex steroids [49]. Single-cell layer dysfunctions could hurt human fertility and be a causative issue in the pathophysiology of vascular disease [50].

T2DM hurts fertility through endothelial dysfunction, IR, chronic low-grade inflammation, and oxidative stress brought on by chronic hyperglycemia. These interrelated mechanisms harm oocytes and spermatozoa, disrupt gametogenesis, and decrease the perfusion of the reproductive tract, which ultimately results in infertility in both sexes.

T2DM impact on female infertility

The intricate interaction of genetic, hormonal, environmental, and behavioral factors that contribute to reproductive issues makes evaluating and diagnosing female infertility an inherent issue. Globally, it is thought to impact 8–12% of women who are of reproductive age, and its incidence varies according to socioeconomic, cultural, and geographic factors [51]. In female reproductive physiology, the hypothalamic-pituitary-ovarian (HPO) axis is a complicated endocrine connection. Following a pulsatile creation of gonadotropin-releasing hormone (GnRH) in the hypothalamus, this axis mediates the cyclic generation of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In order to choose a dominant follicle and prepare the uterine wall for implantation, this occurrence is strictly controlled [52]. An increasing body of research indicates that type 2 diabetes damages the female reproductive system and reduces fertility [53]. For example, in 2021, the southernmost region of Sweden undertook a global cohort study utilizing the Skane Healthcare register spanning the previous 20 years. comparing women between the ages of 18 and 45 who had been clinically diagnosed with type 2 diabetes before their first childbirth, miscarriage, or infertility diagnosis with a group of women seeking medical attention who did not have diabetes of any kind. According to their research, females with T2DM were less likely to have children and had a lower birth rate than women without the disease. They also had a greater chance of miscarriage and infertility during their reproductive journey [54].

As stated above in the mechanism, type 2 diabetes mellitus causes hormonal and metabolic abnormalities that hurt female infertility. Ovulation and endometrial function are disrupted, and it is most commonly associated with PCOS, hyperinsulinemia, obesity, hyperandrogenism, and oxidative stress (Figure 3 and Table 1).

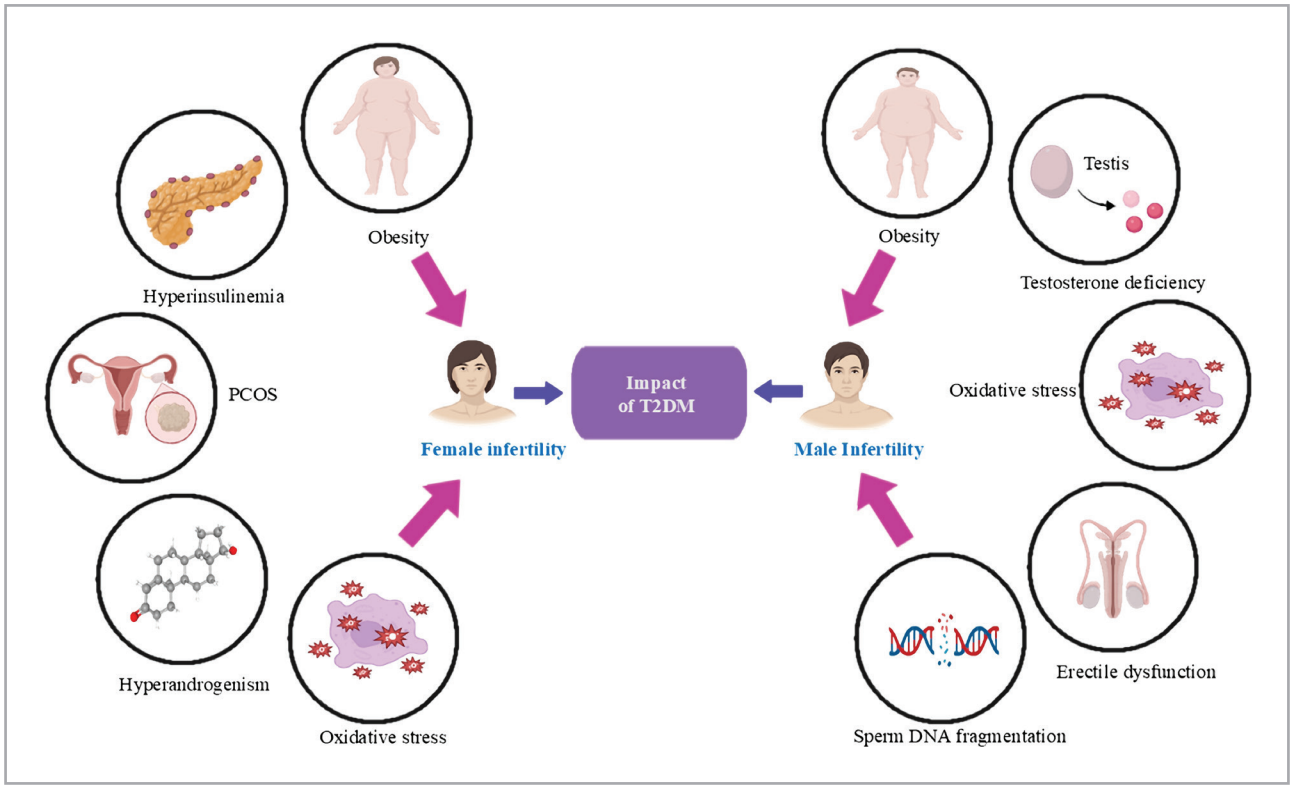

Figure 3: T2DM impact on female and male infertility.

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Table 1: Gender based comparison of T2DM-related infertility.

Gender	T2DM impact on infertility	Conditions	References
Female	Metabolic abnormalities like insulin resistance and hormonal imbalance.	PCOS	[56]
	Anovulation and endometrial disruptions, reduced ovarian insulin receptors,	Hyperinsulinemia	[58, 59]
	Peripheral insulin resistance and reduced β-cell insulin, dysregulated hormone profile.	Obesity	[61, 62]
	Overexpression of IGF-1 receptors, increased production of ovarian androgens.	Hyperandrogenism	[64]
	Excess ROS affects reproductive function, oxidative stress impairs the ovary, leading to endometriosis, DNA fragmentation etc.	Oxidative stress	[65]
Male	Lower levels of NO and cGMP molecules, reduced chance of fertilization.	Erectile dysfunction	[70]
	Impact on oxidative equilibrium, deficiency of testosterone, and inability to generate sperm.	Hypogonadism	[73]
	Declination of the androgen and testosterone levels, Sertoli cell dysfunction.	Obesity	[76]
	Elevated ROS levels lead to the destruction of the sperm.	Oxidative stress	[79]
	Free radicals cause the DNA of the sperm to break, leading to fragmentation.	Sperm DNA fragmentation	[80]

PCOS

There appears to be a reciprocal association between PCOS and T2DM. A new meta-analysis estimates that 21% of women with type II diabetes worldwide have PCOS, irrespective of age. Compared to teenagers, women with T2DM diagnosed at reproductive age had a higher prevalence of PCOS [55]. Typically, women with PCOS have normal levels of FSH but high blood concentrations of testosterone and, less often, excessive levels of LH. Crucially, PCOS is also related to metabolic anomalies, the most prevalent of which is insulin resistance, and this profile has long-term health implications. Overall, PCOS is a reproductive issue and a metabolic disorder [56]. PCOS is frequently linked to infertility and is the main cause of hyperandrogenism and oligo-anovulation in people of reproductive age [57].

Hyperinsulinemia

Hyperinsulinemia impacts both theca and granulosa cells. The LH promotes an early reaction in the granulosa cells of tiny follicles and premature differentiation of theca cells as a result of hyperinsulinemia. It therefore results in anovulation. This can cause implantation problems and negatively impact endometrial functioning in addition to ovulatory disruptions [58]. Endogenous hyperinsulinemia is the driving factor of hyperandrogenism in type 2 diabetes. It has been demonstrated that hyperinsulinemia reduces the expression of ovarian insulin receptors in systemic insulin resistance, although the effect of ovarian insulin on steroidogenesis appears to be maintained [59]. Infertility could be exacerbated by hyperinsulinemia. Insulin plays a significant part in ovulation and ovarian steroidogenesis [60].

Obesity

An inevitable contributing factor to the rising incidence of T2DM is obesity. The hallmarks of T2DM include peripheral insulin resistance and poor β-cell insulin release, which raise fatty acid levels [61]. Increased peripheral aromatization of androgens to estrogens in obese women affects gonadotropin production. In addition, leptin levels rise while growth hormone (GH), sex hormone-binding globulin (SHBG), and insulin-like growth factor binding proteins (IGFBP) drop. Therefore, the HPO axis neuroregulation may be seriously disrupted, and obesity raises the risk of miscarriage, unfavorable pregnancy outcomes, and impaired fetal

development [62]. It has been demonstrated that women who are obese have a threefold increased chance of infertility compared to those who are not [63].

Hyperandrogenism

T2DM impairs normal ovarian function because hyperinsulinemia and insulin resistance cause IGF-1 to be overproduced and hybrid insulin/IGF-1 receptors to be overexpressed. This leads to the development of larger ovaries with numerous tiny follicles (polycystic ovarian morphology), aberrant folliculogenesis, and stimulation of ovarian granulosa cells. As insulin continues to function on the ovary, the overactivity of IGF receptors increases the production of ovarian androgens, which causes clinical hyperandrogenism in females with T2DM. Furthermore, the recruitment of one dominant follicle is inhibited by high insulin concentrations, which act as a gonadotropin on the ovaries' theca cells, resulting in irregular periods [64].

Oxidative stress

Early embryonic development requires a certain level of oxidative stress. Its impacts in the ovary are linked to endometriosis or polycystic ovarian syndrome, and DNA fragmentation and fertilization are compromised in the mitochondrial function of the oocyte. Oocyte development and maturation are not at their peak due to changes in mitochondrial activity. Reactive oxygen species have been linked to placental abnormalities, miscarriages, low implantation rates, and poor-quality embryos [65].

Collectively, all of the aforementioned variables work together to disrupt the HPO axis in women with type 2 diabetes. Both ovulation and endometrial receptivity are compromised by these disruptions. They significantly raise the likelihood of female infertility when combined.

T2DM impact on male infertility

Numerous physiological systems and tissues, including the male reproductive organs, are significantly impacted by type 2 diabetes. A growing number of young and middle-aged males are battling type 2 diabetes during their reproductive years, since the age of those with the diagnosis has been steadily declining in recent years. The World Health Organization reports that infertility, which has a frequency of between 10% and 15% has gradually developed into a public health issue. The male factor is a significant contributing element to about 40% of cases of infertility [66]. For example, A study on local factors in Qatari men was conducted in order to determine the prevalence of infertility with T2DM and to investigate the association between the two conditions. They studied men who had been married for at least a year and were between the ages of 25 and 60. An analysis of 857 male samples revealed that 35.1% of Qatari T2DM men had infertility [67]. A key factor in controlling male fertility is the hypothalamic-pituitary-gonadal (HPG) axis. The anterior pituitary gland secretes gonadotropins, LH and FSH, in response to GnRH, which is produced by the hypothalamus. FSH accelerates spermatogonial development by acting on the Sertoli cells. Testosterone is synthesized and released by Leydig cells in response to LH [68]. T2DM can impact male fertility by inducing dysregulated spermatogenesis, erectile dysfunction, and ejaculation problems (Figure 3 and Table 1) [69].

Erectile dysfunction

The inability to achieve or sustain an erection strong enough for intercourse is known as Erectile dysfunction (ED). Numerous hypothesized mechanisms such as increased AGEs, raised oxygen free radical levels, impaired Nitric oxide (NO) synthesis and impaired cyclic guanosine monophosphate (cGMP)-dependent protein kinase-1 have played a role in ED in diabetic subjects. Reduced NO and its effector molecule, cGMP are recognized to have a major role in the progression of ED in patients with diabetes [70]. ED is prevalent in men with DM, mostly in those with T2DM, which affects between 34% and 45% of men with the disease [71].

Hypogonadism (testosterone deficiency)

Testosterone is essential for the appropriate development of sperm and the growth of male reproductive structures including the prostate and testes in males [72]. Oxidative equilibrium and energy metabolism are directly impacted by testosterone. When faced with a dominance threat, testosterone controls the acute HPA (hypothalamic-pituitary-adrenal axis) reaction. A man's inability to generate either sperm, testosterone or both is called male hypogonadism or testosterone deficiency. Research shows that around one in four men with T2D have hypogonadism or low testosterone levels [73].

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Obesity

Among the numerous physical, psychological, and social disorders associated with obesity, T2DM may be the most catastrophic [74]. Males with higher BMI have been shown to have lower amounts of hormones involved in controlling spermatogenesis and Sertoli cell activity, such as FSH/LH ratios, inhibin B and SHBG [75]. Thus, it is still possible that the lower sperm counts seen in male obesity are caused at least in part by modifications to the HPG axis via estrogen and testosterone as well as probably impaired Sertoli cell function. Lower levels of both free and total testosterone are linked to male obesity. The degree of obesity is directly correlated with this decline in androgen levels [76]. A growing body of research also suggests that male factor infertility is linked to other intrinsic health factors, including obesity, metabolic disorders and sedentary lifestyles [77].

Oxidative stress

ROS is closely linked to male infertility. The sperm cells are extremely vulnerable to oxidative damage. However, these cells are exposed to lipid peroxidation due to ROS because their cytoplasmic membranes are rich in unsaturated fatty acids [78]. The acrosomal response, sperm capacitation, hyperactivation, and sperm–ovule fertilization all require low ROS levels. Nevertheless, OS is brought on by elevated ROS levels that deactivate antioxidants in the serum plasma. In 30 to 80% of infertile men, ROS-induced sperm destruction is the primary cause of infertility, and these disorders ultimately harm mitochondrial and nuclear DNA [79].

Sperm DNA fragmentation

According to certain research, the DNA of sperm breaks apart due to free radicals. DNA fragmentation and crosslinking, together with the start of pyrimidine, purine, and deoxyribose, are the systems that cause sperm DNA fragmentation. Infertility results from the sperm becoming non-functional once DNA fragmentation of the sperm occurs [80].

In the framework of type 2 diabetes, oxidative, hormonal, and metabolic abnormalities interact intricately to cause male infertility. The conditions listed above that interfere with normal testicular function are frequently linked to T2DM. Together, these changes increase the risk of male infertility.

Genetics and epigenetics

It is generally known that T2DM runs in families and that both genetic and environmental variables influence a person's risk of getting the disease. Nonetheless, estimates of heritability have ranged from 25% to 80%. The longest follow-up periods are associated with the highest estimations. Those who have one parent with T2DM have a 40% lifetime risk of getting the disease, while those who have both parents affected have a nearly 70% chance [81].

The pathogenesis of type 2 DM and infertility has been linked to several genes, including PPARG, IRS-1 and 2 and SHBG. Important functions like steroidogenesis, glucose metabolism, and insulin signaling are regulated by these genes. IR and β-cell dysfunction cause these pathways to become dysregulated, which leads to hormonal imbalance, poor gametogenesis, and decreased fertility in both men and women. Therefore, a crucial connection between type 2 diabetes and reproductive failure may be genetic changes in metabolic pathways.

PPARG gene

PPARG is a ligand-dependent transcription factor that is a participant of the nuclear hormone receptor superfamily. The networks of gene expression required for cell division, proliferation, morphogenesis, and metabolic balance are regulated by PPARγ. Additionally, PPARγ is a crucial transcriptional regulator that controls inflammatory reactions, lipid metabolism, and glucose levels in cells [82]. Moreover, in women, PPARγ can influence steroidogenesis by reducing the theca cells' synthesis of androgenic precursors and counteracting the stimulation of androstenedione, which is usually brought on by the combination of LH and insulin in conditions like hyperinsulinism, PCOS and Oligo-ovulation [83]. In men, PPARγ is a crucial molecule that controls energy homeostasis. It is affected by the HPG axis and is in turn controlled by the HPG. Male infertility is caused by changes in testicular steroidogenesis and spermatogenesis brought on by inflammation. According to certain theories, PPARG transcriptional activity disrupts the expression of androgen and estrogen receptors, as well as testicular steroidogenesis and ROS metabolism [84].

IRS–1 and *2* gene

Insulin receptors are made up of two α and two β-dimers. The α-subunit covers the ligand-binding

site, whereas the β-subunit covers the ligand-activated tyrosine kinase. Following insulin's binding to its receptor, tyrosine is phosphorylated, phosphorylating the intracellular substrates IRS-1 and 2. To regulate metabolism and take part in the mitogenic effects of insulin, IRS-1 and 2 then unite and activate downstream effectors such as phosphoinositide 3-kinase. It was proposed that IR, T2DM, and PCOS in women were associated with the most prevalent variation, IRS-1 rs1801278G>A polymorphism [85]. When the insulin family of receptors is absent, male sex determination during embryonic development is suppressed [86].

SBHG gene

SHBG is a glycated homodimeric plasma transport protein that is mostly produced in the liver. It has a greater affinity than estradiol for binding the androgens testosterone and dihydrotestosterone (DHT) [87]. Ding and colleagues present a sexually dimorphic association between testosterone and the likelihood of developing T2DM in a comprehensive systemic review and meta-analysis that included both sexes. Men who have diabetes are more likely to have lower testosterone levels, whereas women who have greater testosterone levels are more likely to have diabetes [88].

Epigenetics

The term "epigenetics" describes heritable modifications to gene function that take place independently of nucleotide sequence changes. DNA-methylation, histone acetylation, and non-coding RNAs are examples of mechanisms that cells utilize to control gene expression in response to environmental stimuli. These mechanisms can last a person's lifetime and be passed down through two to three generations [89]. Furthermore, epigenetics established a biological connection between environmental variables and T2D. The mechanism of T2D and other conditions allied with complex metabolism has also been revealed to be influenced by epigenetics, namely DNA methylation, which alters gene expression [90].

Since impaired DNA methylation interferes with the regular control of gene expression required for reproductive health, it plays a major part in female infertility. Genes involved in crucial reproductive activities may become dysregulated as a result of atypical methylation patterns, including hypermethylation or hypomethylation. Infertility and endometriosis are caused by hypermethylation in the HOXA10 promoter region, which decreases expression and is necessary for endometrial receptivity and implantation. PCOS causes hormonal abnormalities that affect ovarian function because hypomethylation of the CYP19A1 gene promoter promotes the production of estrogen. Male fertility depends on DNA methylation, which confirms the appropriate gene expression needed for spermatogenesis. Deviations from normal DNA methylation patterns could damage sperm development and function, which would finally result in infertility. Changes in DNA methylation patterns have been discovered in several genes that are strongly connected with infertility [91].

T2DM is largely caused by genetic vulnerability, with multiple loci including PPARG, IRS-1 and 2, and SHBG, which are involved in essential tasks like steroidogenesis and insulin signaling. Male and female infertility may result from interruptions in these pathways, which could affect the regulation of reproductive hormones. Together with static genetic variations, epigenetic changes, particularly DNA methylation, have become dynamic modulators of gene expression in response to metabolic stress associated with T2DM. The collective effects of these interconnected genetic and epigenetic abnormalities offer a mechanistic explanation for the reproductive issues seen in people with T2DM.

Clinical implications and management

One of the first-line approaches for managing type 2 diabetes is lifestyle modification, which includes losing weight, getting more exercise, and changing to a healthier diet [92]. An integrated approach that includes both pharmacological treatments and lifestyle-based, non-pharmacological interventions is necessary for the management of infertility caused by type 2 diabetes. To maximize fertility outcomes, a balanced strategy addressing metabolic and reproductive dysfunctions is necessary.

Non-pharmacological management

Exercise

The management of T2DM may benefit from physical activity. Crucially, current research indicates that the type of exercise is just as significant as the activity itself. In those with type 2 diabetes, regular resistance training has been demonstrated to enhance muscle function, insulin sensitivity, and glycemic management. When it comes to controlling blood glucose levels

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and improving general metabolic health, combining aerobic and resistance training seems to be more beneficial than single-mode training [93].

Healthy diet

The Mediterranean diet is a useful dietary intervention for enhancing glycemic control, according to the meta-analysis, and the low-carb diet had the best anthropometric results in people with T2D and concurrent overweight or obesity [94].

Bariatric surgery

It has been discovered that several surgical techniques collectively referred to as bariatric surgery or metabolic surgery, which were first suggested as a means of treating morbid obesity, are also useful in the prevention and management of T2D. In patients undergoing bariatric surgery, some of the mechanisms that are crucial for the control and remission of type 2 diabetes include improvements in insulin production, an increase in beta cell mass, and modifications to the gut microbiota [95].

Pharmacological management

Metformin

Metformin (MF) is the oldest insulin sensitizer used to treat type 2 diabetes mellitus and the most commonly prescribed medication for reproductive problems linked to insulin resistance. Its effect lowers glucose concentrations without the danger of hypoglycemia by improving peripheral glucose uptake, increasing tissue insulin sensitivity, and decreasing hepatic glucose output [96].

MF lowers insulin secretion and hepatic gluconeogenesis, prevents body weight gain, and lowers the risk of hypoglycemia. In individuals with PCOS and type II diabetes, metformin is often administered as a stand-alone medication to trigger ovulation or as a supplement to fertility treatments, both before and throughout pregnancy [97]. The restorative effect of MF on spermatogenic function and hormonal indices of the HPG axis in 45 males with MetS who had impaired spermatogenesis was investigated by Giuseppe Morgante and associates. It enhanced the motility and morphology of spermatozoa, which led to a partial restoration of fertility. Additionally, blood levels of LH and testosterone were markedly elevated, whereas those of SHBG and estradiol were markedly reduced. This resulted in a rise in the ratio of testosterone to estradiol and an improvement in androgenic status [98].

To sum up, non-pharmacological methods, including exercise, nutrition, and bariatric surgery enhance metabolic health and have a favorable impact on reproductive results. Metformin is the preferred pharmacological agent due to its dual role, as it supports reproductive function and improves insulin sensitivity. To manage type 2 diabetes and infertility in both sexes, these interventions provide a holistic approach.

Research gaps and future directions

Merely a few studies have prospectively investigated the correlation between the occurrence of T2D in females and overall infertility. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of Dutch women did not find an association between T2D risk and seeking counsel for infertility issues [99]. Nevertheless, self-reporting of fertility issues was gathered at baseline at an average age of 57 years, and this analysis involved both dominant and incident cases of diabetes. There is contradictory evidence in the literature about the association between diabetes risk and nulliparity, a possible indicator of infertility. Some studies indicate that nulliparous women are more at risk than parous women [100]. However, limited studies have been done on the genome-level DNA methylation pattern in spermatozoa from people with type 2 diabetes [101].

Considerable progress has been made in recent years in comprehending the pathophysiological underpinnings of type 2 diabetes. Nonetheless, precision medicine still faces difficulties due to its range and complications. The notion of Precision Medicine (PM) places a strong emphasis on customizing treatment plans according to a patient's genetic makeup, lifestyle, environment, and the unique molecular causes of their illness. According to precision medicine, upcoming studies on the pathophysiology of type 2 diabetes will progressively emphasize in-depth investigation at the molecular mechanism level, precision, and customisation [102]. AI advances the treatment of type 2 diabetes by enabling real-time monitoring of blood glucose levels, exercise, and food using smart devices. AI then delivers recommendations for tailored health management [103].

Initial findings on sizeable sample cohorts showed that low molecular weight heparin effectively prevented spontaneous abortion, and genetic indicators were associated with spontaneous ovulation in PCOS individuals. Anti-Mullerian hormone (AMH) levels and

antral follicle count (AFC) are the foremost clinically accessible biomarkers for regulating gonadotropin dosage [104]. In the pursuit of precise PM targets, antioxidants are taken into account when treating male infertility. It claims that an antioxidant therapy program will benefit couples' reproductive health and increase their comprehension of their infertility [105].

To summarize, significant research gaps remain in understanding the common processes of T2DM and infertility, especially when it comes to sex-specific issues. Future directions focus on combining molecular biomarkers and precision medicine to enable tailored approaches to the treatment of both disorders.

Conclusion

Infertility in T2DM results from complex disruptions in insulin resistance, glucose metabolism, and chronic inflammation, leading to impaired oxidative balance, vascular integrity, and hormonal regulation. These changes reduce endometrial receptivity, impair ovarian function, increase miscarriage risk in women, and cause erectile dysfunction, testosterone deficiency, and abnormal sperm parameters in men. Molecular contributors such as IRS-1/2, SHBG, and PPARG act as shared genetic links between T2DM and reproductive decline by altering insulin signaling, steroidogenesis, and gametogenesis. Epigenetic modifications, including altered DNA methylation patterns, further perpetuate the heritable effects of metabolic dysfunction on fertility. Addressing T2DM-related infertility requires a precision medicine approach integrating optimal glycemic control, anti-inflammatory interventions, lifestyle modification, and biomarker-driven personalization of reproductive therapies. Early screening for reproductive dysfunction in T2DM patients, coupled with multidisciplinary care involving endocrinologists, reproductive specialists, and genetic counselors, can optimize outcomes. Such targeted strategies not only improve fertility potential but also reduce long-term metabolic and cardiovascular risks, providing a dual benefit for public health and patient well-being.

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Conflict of interest

The authors declare no conflict of interest.

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