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Diabetes mellitus–induced disruptions of male reproductive functions: A comprehensive review

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ABSTRACT

Diabetes mellitus has emerged as a widespread global health concern, contributing significantly to morbidity and mortality rates. The metabolic disturbances associated with diabetes can adversely impact the male reproductive system, leading to reduced fertility. This review offers an in-depth evaluation of recent global research exploring the impact of diabetes on male reproductive health. Relevant experimental and clinical studies were identified, with a focus on diabetes-related effects on reproductive organs, hormones, and sexual function. The review highlights that insulin deficiency and resistance in diabetic conditions disrupt the hypothalamic-pituitary-gonadal axis, reducing levels of key reproductive hormones such as gonadotropin releasing hormone, luteinizing hormone, follicle stimulating hormone, and testosterone. These hormonal disruptions lead to structural and functional damage in reproductive organs including the testes, Sertoli cells, epididymis, sperm, and accessory glands. Moreover, diabetes contributes to erectile and ejaculatory dysfunctions. Various pathophysiological mechanisms such as oxidative stress, hormonal imbalances, germ cell apoptosis, autophagy, mitochondrial dysfunction, and endoplasmic reticulum stress are identified as underlying contributors to diabetes-induced male infertility. The findings of this review provide valuable insights into the complex mechanisms by which diabetes affects the male reproductive function. By integrating current research, it highlights the critical need for further studies and the development of targeted therapies to effectively address diabetes-induced infertility.

KEYWORDS: Diabetes mellitus; Male reproductive function; Insulin; Sperm parameters; Infertility; Oxidative stress

1. Introduction

Diabetes, a chronic metabolic disease defined by raised blood sugar levels due to inadequate insulin synthesis or impaired insulin action, is often accompanied by dysfunction in pancreatic beta

cells[1]. The global incidence of diabetes has surged significantly in current years, posing a critical public health challenge[2]. In 2021, projected 573 million population aged between 20-79 had diabetes, by 2030, that figure is expected to increase to 643 million and by 2045, it may reach 783 million[3].

Diabetes mellitus (DM) is broadly categorized into two main types: Type I and Type II. Both types involve disruptions in the metabolism of carbohydrates, lipids, and proteins. Type I diabetes mellitus (T1DM) affects approximately 422 million people worldwide, approximately 10% have T1DM. Roughly 85% of these cases are diagnosed before the age of 20, while at least 15% occur in adults aged 30 or older. T1DM arises from autoimmune-mediated or injury-induced destruction of pancreatic beta cells. Factors such as genetics, ethnicity, age, and gender influence susceptibility of damaging insulin-producing cells[4]. The disease can develop rapidly over days or weeks and typically progresses through: Reduced insulin levels, increased reliance on lipids for energy and the liver's manufacture of cholesterol, and depletion of the body's proteins[5].

Type II diabetes mellitus (T2DM) is becoming increasingly prevalent worldwide, accounting for 90%-95% of diabetes cases. While it was traditionally associated with adults and older individuals, its incidence among younger populations has surged over recent years, indicating a likely rise in future prevalence. This form of DM results from reduced sensitivity of target

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tissues to insulin's metabolic actions. Commonly known as a “modern disease,” it is primarily influenced by lifestyle factors such as poor dietary habits and being overweight. Unlike T1DM, Type II is frequently linked to raise insulin levels in the blood, or hyperinsulinemia[4]. In 2016, projections indicated that the prevalence of Type II diabetes among individuals aged 20-79 would increase by 71.5% by 2035. Regional estimates predicted growth rates of 6.0% (Africa), 7.1% (Europe), 11.3% (Middle East), 12.3% (North America and the Caribbean), 8.2% (South and Central America), 9.4% (Southeast Asia), and 8.4% (Western Pacific)[6].

During pregnancy, glucose intolerance usually appears in the third trimester and is known as gestational diabetes mellitus (GDM). At least six weeks after giving birth, women with GDM should have an oral glucose tolerance test to determine their diabetic conditions. Although its frequency can rise dramatically in groups with a higher propensity for type 2 diabetes, GDM affects 8%–9% of pregnancies[7].

Various pathophysiological factors contribute to the disease, including elevated blood glucose levels, abnormal lipid profiles, high blood pressure, oxidative damage, chronic inflammation, and cellular stress affecting the mitochondria and endoplasmic reproductive system, such as disturbances in the hypothalamic-pituitary-gonadal axis (HPGA) and reduced testosterone production. These interconnected mechanisms contribute to macrovascular, microvascular dysfunctions and neuropathic complications[8], ultimately leading to damage, dysfunction, or even failure of various organs and tissues. Studies on human and animal populations with diabetes reveal that the condition significantly contributes to testicular dysfunction, reduced sperm production, abnormal erections, ejaculatory disturbances, and overall male infertility[9].

This review offers an in-depth analysis of the multifaceted impact of DM on male reproductive health. The novelty of this review lies in its integrative approach, systematically detailing the potential mechanisms through which diabetes contributes to reproductive dysfunctions, alongside a clear exposition of the disease's correlation with male reproductive parameters. By including comparative summaries in tabular form, the review distinctly highlights findings from both animal models and human studies offering a unique translational perspective that bridges experimental research with clinical observations. Despite growing interest in this field, a significant research gap remains in understanding the precise molecular pathways and long-term clinical consequences of diabetes-related reproductive impairments, especially in humans. Furthermore, limited studies explore the potential reversibility of these effects or the efficacy of therapeutic interventions targeting reproductive outcomes in diabetic patients. This review not only consolidates current knowledge but also highlights the pressing need for longitudinal and mechanistic studies to inform future research directions and improve clinical management strategies.

2. Methods

This review was carried out *via* a systematic literature survey aimed at gathering and analysing scientific information on DM-induced disruptions of male reproductive functions. A comprehensive search was conducted across several databases, including Scopus, PubMed, Google Scholar, and Web of Science, to identify all relevant English-language publications that were available from January 2014 to December 2024. Additionally, a few important earlier studies were incorporated in the introduction and mechanism of action sections to provide better context and explanation.

Search terms included “effect of diabetes on testicular function,” “epididymal function,” “sperm quality,” “accessory gland function,” “erectile function,” and “ejaculatory function.” Studies exploring the pathophysiology and molecular mechanisms underlying these effects were included, with particular focus on processes such as insulin deficiency, insulin resistance, oxidative stress, disruption of the hypothalamic–pituitary–gonadal (HPG) axis, germ cell apoptosis, endoplasmic reticulum stress, mitochondrial dysfunction, germ cell autophagy, and chronic inflammation. Both experimental and clinical studies relevant to these aspects were reviewed to ensure comprehensive coverage of the impact of diabetes on male reproductive health.

Inclusion criteria were: 1) Access was focused on full-text articles in English or those in other languages with available English translations; 2) Studies investigating the effect of diabetes-induced reproductive dysfunction in experimental animal models; 3) Studies examining the impact of diabetes on male reproductive function in human patients. Exclusion criteria were: 1) Articles not published in English or those for which reliable English translations were unavailable; 2) Duplicate publications and general review articles that did not offer unique insights or relevant context; 3) Articles were excluded if they lacked sufficient information, including missing methodological details, incomplete data, or relevant outcomes. Additionally, studies for which only the abstract was available and the full text could not be accessed were also excluded.

3. Impact of diabetes on male reproductive functions

DM results from a complete absence or a relative deficiency of insulin, or from insulin resistance, impairing the body's ability to regulate glucose effectively. This leads to metabolic imbalances and persistent hyperglycemia, which can cause complications like diabetic neuropathy and vascular damage. Research indicates that nearly half of diabetic men suffer from reduced semen quality and compromised reproductive function. Studies in both animal models (Table 1) and humans (Table 2) reveal that diabetes adversely affects the functions of the testes, epididymis, and accessory

Table 1. Effects of diabetes mellitus on male reproductive function in different animal models.

Animal model	Duration of experiment	Effects on reproductive functions	References
Streptozotocin (STZ)-induced rats	5 weeks	In diabetic rats, reduced seminiferous tubule diameter, thickened basement membranes, and germ cell degeneration were observed, along with decreased vascular endothelial growth factor (VEGF) and nerve growth factor beta (NGF- β) levels and increased VEGF + terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL)-positive cells, indicating enhanced apoptosis.	[17]
STZ-induced mice	1 day, 1 week and 4 weeks	Western blot showed no change in phosphorylated H2A histone family member X (γ H2AX) expression at any time point after low-dose STZ treatment, indicating no sperm DNA damage, though paternal prediabetes altered sperm cytosine methylation patterns.	[34]
STZ-induced rats	90 days	Diabetes induces spermatotoxicity, oxidative stress, and poly (ADP-Ribose) polymerase (PARP) 1-linked DNA damage in the rat testis.	[51]
STZ-induced rats	8 weeks	Diabetes impaired the prostate by reducing mast cells, epithelial height, and androgen receptor expression while increasing apoptosis, with these effects being reversed by insulin and testosterone treatment.	[40]
STZ-induced rats	28 days	Diabetes in rats caused epididymal alterations such as reduced epithelial height, increased fibromuscular thickness, and epithelial vacuolization.	[25]
STZ-induced diabetic rats	8 weeks	Diabetic rats showed altered Leydig cell morphology with reduced size, increased number, and decreased body as well as testis weight.	[18]
STZ-induced rats	28 days	Diabetic rats showed reduced sperm quality, testosterone, steroidogenic acute regulatory protein (StAR) and 3 beta-hydroxysteroid dehydrogenase (3 β -HSD) activity, and Sertoli cell vimentin, with increased lipid peroxidation, apoptosis, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), Wnt4 expression, and lower Johnsen's score.	[23]
Mice with type 2 diabetes mellitus (T2DM)	–	In diabetic mice, a reduced intracranial pressure/mean arterial pressure ratio indicated erectile dysfunction (ED). Four miRNAs were implicated in T2DM-related ED by modulating fibrosis, apoptosis, and endothelial nitric oxide synthase (eNOS)/cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathways, with decreased insulin-like growth factor-1 identified as a target of miR-18a and miR-206.	[52]
Neonatal-STZ induced T2DM male Wistar rats	3 months	In T2DM rats, serum and testicular testosterone dropped sharply, sperm motility declined, testicular glycolysis and glycogen metabolism were disrupted, reducing sperm quality.	[22]
STZ-induced male Wistar rat	6 months	In diabetic rats, testicular diameters and volume were significantly reduced ($P < 0.05$) compared to the controls.	[53]
STZ-induced mice	14 days	Diabetic mice showed reduced sperm count and seminiferous tubule epithelial vacuolization.	[54]
Mice with T2DM	–	Sperm from diabetic mice showed altered mRNA and lncRNA expression, with affected mRNAs linked to diabetes-related pathways.	[33]
STZ-induced rats	8 weeks	Diabetic testes showed reduced androgen-binding protein (ABP), inhibin, and testosterone, increased TUNEL-positive cells, and lower Johnsen scores, while transferrin remained unchanged.	[55]
STZ-induced rats	1 week, 1 and 6 months	Diabetic rats showed significant reductions in serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone at 1 and 6 months, indicating progressive hormonal disruption.	[20]
STZ-induced rats	8 weeks	Diabetic rats exhibited lower testis weight and testosterone, elevated calcium-sensing receptor (CaSR) and malondialdehyde (MDA), reduced superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), increased germ cell apoptosis, decreased Bcl-2, and increased Bax and Caspase-3.	[21]
STZ-induced male rats	43 days	Diabetic rats showed reduced testicular size, lower testosterone and estradiol, and delayed preputial separation compared to treatment groups.	[56]
STZ-induced male Wistar rats	8 weeks	STZ-treated rats showed reduced normal sperm and seminiferous tubule sperm, with STZ-60 causing complete loss of spermiogenesis.	[57]
STZ-induced male albino Wistar rats	60 days	STZ-40 and STZ-60 mg/kg rats had reduced body and reproductive organ weights, testosterone, sperm count, and antioxidants; STZ-60 mg/kg also showed lower testicular glutathione, higher glucose, increased MDA and GSH-Px, and severe testicular damage.	[58]
STZ-induced diabetic rats	–	T2DM reduces testicular VEGF via the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, impairing microcirculation and causing testicular structural and functional dysfunction.	[59]
Diabetic heterozygous <i>Ins2Akita</i> ^{+/-} (<i>Ins2Akita</i>) mice	–	In diabetic mice, hyperglycemia activated protein kinase C (PKC) and polyol pathways in the testes, raising advanced glycation end-products (AGE) markers and receptor expression. AGEs minimally affected extracellular signal-regulated kinase 2 (ERK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and nuclear factor erythroid 2-related factor 2 (Nrf-2) but activated CDC42 and Akt1, revealing two main hyperglycemia-induced testicular damage pathways.	[60]
STZ-induced diabetic rats	8 weeks	Hyperglycemic male rats showed reduced intromission frequency, ejaculatory latency, and post ejaculatory interval, along with lower penis and testis weights, decreased sperm counts, and increased sperm abnormalities.	[61]

Table 1. Continued.

Animal model	Duration of experiment	Effects on reproductive functions	References
STZ-induced diabetic rats	24 and 48 days	At 24 and 48 days, diabetic rats had lower testis and epididymis weights, reduced seminiferous tubule diameter, and smaller epididymal tubular area.	[29]
STZ-induced Sprague–Dawley rats	16 weeks	In the diabetes mellitus (DM) group, epididymal ducts showed fatty vacuolization, damaged stereocilia, inflammation, and interstitial hyperplasia, with transmission electron microscope revealing enlarged mitochondria, vacuoles, and partial stereocilia loss.	[44]
Spontaneously diabetic torii male rats	–	In diabetic rats, there was a high incidence of Leydig cell hyperplasia and Leydig cell tumors (LCH/LCTs), with elevated extracellular matrix proteins (vitronectin, fibronectin, tenascin) and integrins ($\alpha 4$, $\alpha 5$, $\alpha v \beta 1$, $\beta 1$, $\alpha v \beta 3$) compared to normal seminiferous tubules.	[62]
Alloxan-induced diabetic mice	40 days	In diabetic mice, testosterone, FSH, LH, and healthy motile sperm were significantly reduced ($P < 0.001$), with seminiferous tubule atrophy, widened inter-tubular spaces, interstitial loss, tubular degeneration, and nearly absent epididymal sperm.	[63]
STZ-induced male albino Wistar rats	8 weeks	STZ-30 and STZ-60 mg/kg rats had reduced motile sperm, with increased c-Jun N-terminal kinase (JNK) and caspase-3 and slight p38 MAPK, caspase-7, and PARP activation, indicating AGE-receptor for advanced glycation end product (RAGE)-MAPK-mediated sperm dysfunction.	[64]
STZ-induced male Wistar rats	4 weeks	Hyperglycemia alters Sertoli cell metabolism, significantly increasing expression of lactate transporter (MCT4), glucose transporters (GLUT1, GLUT3), and antioxidant proteins (Nrf2, catalase) at 2 and 4 weeks.	[24]
STZ-induced mice	8 weeks	STZ-induced diabetes caused reproductive dysfunction, reducing brain GnRH-I, estrogen receptor α (ER α), testicular ER α , testosterone, estradiol, testis weight, and volume.	[65]

Table 2. Effects of diabetes mellitus on male reproductive function in humans.

Patients	Average age	Effects on reproductive health	References
158 patients with type 2 diabetes mellitus (T2DM)	40 and 75 years	Sexual dysfunction affects 68.5% (men) and 70% (women) with T2DM, with higher rates in older adults, those with severe depression, and men with comorbidities.	[66]
1 260 T2DM patients	64 years and older	Baseline serum testosterone and sex hormone-binding globulin (SHBG) levels were significantly lower in T2DM patients ($n=30$) than in non-diabetic individuals.	[67]
80 patients of infertility clinic	18–40 years with insulin resistance (IR) and 18–39 years (without IR)	The survey concluded that IR in MetS impairs male fertility <i>via</i> hyperinsulinemia and disrupted glucose uptake, as seen in T2DM.	[68]
503 T2DM patients	(58.0 $\pm$ 8.9) years	In newly diagnosed T2DM patients, 19.4% had mild erectile dysfunction (ED), while 28.3%, 32.9%, and 58.4% experienced low sexual desire, delayed ejaculation, and premature ejaculation (PE), respectively.	[41]
115 T2DM patients	Less than 70 years (mean 56.6 years)	In middle-aged T2DM patients, low testosterone is associated with advanced atherosclerosis, showing a negative correlation with carotid intima-media thickness (IMT) ($r=-0.39$, $P<0.0001$) and increased endothelial dysfunction, C-reactive protein (CRP), and IMT ≥ 0.1 cm.	[69]
376 T2DM patients	<40 years to ≥ 70 years	The study found that ED was significantly associated with age and diabetes duration, but not with glycemic control.	[70]
52 T2DM patients	(36.29 $\pm$ 5.29) years	Diabetic patients showed reduced ejaculate volume, sperm count, motility, hypo-osmotic swelling, and DNA integrity compared to fertile non-diabetics.	[34]
105 T2DM patients	(51.62 $\pm$ 7.76) years	T2DM markedly reduced total, free, and bioactive testosterone, sexual drive, and international index of erectile function (IIEF)-5 scores, while increasing CRP.	[48]
Men diagnosed with diabetes	32 years and 27 years old	Semen analysis revealed reduced ejaculate volume (<1 cc), low pH (<6.7), absence of fructose, and azoospermia.	[71]
32 patients with type 1 diabetes mellitus (T1DM)	27 years	Diabetic patients showed reduced sperm rapid motility, impaired mitochondrial function, and post-ejaculatory epididymal dysfunction.	[72]
81 patients newly diagnosed and 105 previously diagnosed T2DM	–	In T2DM, low total and free testosterone affected 26%–28% and 19%–21% of patients, respectively, with better glycemic control [glycated haemoglobin (HbA1c) $<7\%$] linked to higher total testosterone (TT) and lower deficiency.	[73]
48 healthy men semen sample incubated with D and L-glucose	–	Sperm viability and motility were unaffected by D-glucose at 5, 25, or 50 mM. However, L-glucose significantly reduced motility after the first day, while viability remained unchanged.	[74]
761 T1DM patients	–	Prostate specific antigen (PSA) levels decline with increasing HbA1c in men with T1DM, independent of BMI, age, testosterone, or treatment, suggesting that poor glycemic control may reduce prostate cancer detection by lowering PSA levels.	[75]

Table 2. Continued.

Patients	Average age	Effects on reproductive health	References
94 T2DM patients	30–65 years	About one-third of males with T2DM have hypogonadotropic hypogonadism (HH), linked to a 36% drop in glucose infusion rate (GIR) and reduced expression of key insulin signaling genes (<i>IRb</i> , <i>Akt-2</i> , <i>IRS-1</i> , <i>GLUT4</i>).	[76]
199 T2DM patients	18–65 years	Diabetic men with ED showed higher PE prevalence and shorter ejaculatory latency time (ELT), but HbA1c did not predict PE.	[77]
25 T2DM patients	47.83 years	Diabetic men had lower sperm concentration (24.6 vs. 42.7 million/mL), motility (52.3% vs. 63%), and normal morphology (31.5% vs. 47.2%) than non-diabetics.	[78]
5350 randomly selected men	30–70 years	Reduced SHBG and TT, with unchanged luteinizing hormone (LH) and free testosterone, are linked to higher T2DM risk, with low testosterone serving as an early marker.	[79]
151 T1DM patients	18–35 years	Diabetic men showed a higher incidence of ED, with over half experiencing mild ED. Those with ED had lower body weight, body mass index (BMI), fasting glucose, insulin dose, and high-density lipoprotein cholesterol (HDL), and higher depression scores compared to men without ED.	[80]
25 patients (15 T1DM and 10 T2DM)	(35.84±8.89) years	Diabetic men showed lower seminal zinc and magnesium, which negatively correlated with HbA1c.	[81]
152 T2DM patients	30–50 years	Diabetic infertile patients had lower zinc and magnesium and higher copper in serum and seminal plasma compared to healthy controls.	[82]
213 T2DM patients	(53.25±11.21) years	Hypogonadism is strongly associated with a number of risk factors for diabetes. Homeostasis model assessment for insulin resistance (HOMA-IR), LH, metabolic syndrome (MS), BMI, and other variables are separate indicators of risk for hypogonadism in males with diabetes (type 2).	[47]
100 T2DM patients	(44.5±7.9) years	Diabetic patients had lower serum bioavailable testosterone, follicular stimulating hormone (FSH), LH, prolactin, and SHBG, with hypogonadism more prevalent than in non-diabetics.	[83]
A male with complete absence of ejaculate	19 years old	The patient tested positive for glutamic acid antibody (GAD) and islet antigen 2 (IA2) antibodies, with blood sugar 24.5 mmol/L and HbA1c >15%, confirming T1DM; notably, retrograde ejaculation was the initial symptom.	[84]
30 DM patients	21–49 years	Diabetic men had reduced sperm motility, vitality, survival, morphology, semen volume, pH, and density, with elevated interleukin (IL)-17 and IL-18 linked to glucose levels and sperm DNA damage, suggesting cytokine-mediated infertility.	[35]
38 T1DM patients, 55 T2DM patients	–	Diabetic men face higher infertility risk <i>via</i> different mechanisms: Type 2 diabetes impairs sperm vitality and increases DNA fragmentation through inflammation and oxidative stress, while Type 1 reduces ejaculate volume and motility by affecting epididymal function and mitochondria.	[85]
6 T2DM patients	35 to 50 years	Diabetic individuals showed reduced semen volume, sperm concentration, total count, and impaired sperm tail mitochondrial structure.	[31]
115 T2DM patients	40–80 years	Hypogonadism, mostly secondary, is common in men with T2DM, negatively correlated with waist circumference, BMI, fasting blood glucose (FBG), and triglycerides (TG), positively with HDL, and independently associated with waist circumference and FBG.	[86]
57 T1DM patients	18–50 years	ED affected 28.1% of patients, less severe without nephropathy; retrograde ejaculation occurred in 8.8%. TT was unchanged, SHBG and LH increased, free androgen and testosterone index decreased, FSH unchanged, prolactin higher, and PSA inversely correlated with HbA1c.	[44]
54 T2DM patients	–	No significant differences were observed in FSH, testosterone, or testicular volume between diabetic and non-diabetic groups ($P>0.05$).	[87]
8 T2DM patients	20–45 years	The current study revealed changes in global cytosine methylation patterns in spermatozoa from men with T2DM.	[32]
30 T2DM patients	0–50 years	The statistical evaluation indicated notable reductions in all sperm parameters, including normal morphology, motility (both progressive and non-progressive), concentration, and viability, among men with diabetes than the control group.	[30]
157 male participants	20–45 years	Diabetic men showed reduced sperm concentration, count, progressive motility, testosterone, SOD, and zinc- α 2 glycoprotein (ZAG), with increased FSH, LH, malondialdehyde (MDA), IL-6, α -glucosidase, zinc, and fructose.	[88]
18743 T1DM patients	38–56 years	Multivariate analysis showed each additional year of age raised infertility risk by 5% in men with T1DM; age was the only significant predictor, though kidney damage also increased risk.	[89]
112 T1DM patients	18–30 years	T1DM affects young men with similar sexual dysfunction rates regardless of glucose variability, with ED at 25% and PE at 13%.	[90]
380 T1DM patients	–	Men with T1DM show reduced normal sperm morphology, progressive motility, and seminal volume, with no change in total sperm count or concentration.	[91]
35 DM patients	30–45 years and 36–59 years	Diabetic men showed lower serum FSH, LH, and TT, with higher prolactin and estradiol. Semen analysis revealed reduced sperm count, motility, and abnormal morphology, contributing to sexual dysfunction.	[92]

Table 2. Continued.

Patients	Average age	Effects on reproductive health	References
35 DM patients	30–45 years and 36–59 years	Diabetic men showed lower serum FSH, LH, and TT, with higher prolactin and estradiol. Semen analysis revealed reduced sperm count, motility, and abnormal morphology, contributing to sexual dysfunction.	[92]
915 T2DM patients	–	Findings suggest that well-controlled T2DM may not enhance the likelihood of genetic abnormalities in spermatozoa in the European population.	[93]
54 participants with fertility problem (27 diabetic)	25–50 years	Non-diabetic men had higher semen volume, sperm count, motility, pH, and percentages of live and normal sperm, while diabetic men showed longer liquefaction time and more sluggish and dead sperm.	[94]
88 T1DM patients	18–35 years	Men with T1DM and ED had poorer metabolic profiles and lower semen quality, with higher semen volume, concentration, and count, but fewer rapidly motile sperm, more non-progressive motility, and abnormal morphology.	[95]
680 T2DM patients	–	This study examines the causal relationship between T2DM and male infertility.	[96]

glands, leading to impaired sperm production, maturation, erectile function, and ejaculation. Increasing evidence also associates the growing prevalence of diabetes with declining fertility and birth rates in modern populations[10–12].

3.1. Effect of diabetes on testicular functions

The testes play a key role in testosterone production and sperm generation[13], and maintaining their structural integrity is crucial for proper function[14]. DM has been shown to reduce testicular mass and Leydig cell count, contributing to lower testosterone levels and testicular structural damage[15,16]. Hyperglycemia induces testicular cell death and impairs blood flow, as evidenced by Doppler studies in diabetic rats showing reduced testicular blood velocity due to decreased vascular endothelial growth factor (VEGF) transcription, which affects endothelial cells function and microcirculation[17].

Diabetes also delays gonadal maturation, reduces sexual activity and testosterone production, and causes gonadal atrophy. Histological changes include a higher percentage of empty tubules, degeneration of seminiferous epithelium, and thinning of the spermatogenic layer[10,16]. Sisman *et al* observed reduced seminiferous tubule diameter and basement membrane thickening in diabetic rats[18]. Other studies reported decreased Leydig cell volume, smaller nuclear size, and reductions in testicular size and weight, including vertical, antero-posterior, and transverse diameters in diabetic rats compared to the controls[19,20]. Additionally, diabetic testicular tissue showed increased calcium-sensing receptor (CaSR) expression, elevated malondialdehyde (MDA) levels, reduced superoxide dismutase (SOD) and glutathione peroxidase (GSH-px) activities, and higher rates of germ cell apoptosis[16,21].

3.2. Effect of diabetes on Sertoli cells

Sertoli cells, or nurse cells, are essential for testicular energy metabolism and form a key component of the blood-testis barrier. In the testes, energy production is unique, with lactate serving

as the main fuel for germ cell adenosine triphosphate (ATP) generation[22]. Studies by Rato *et al* showed that Sertoli cells from diabetic rats had increased glucose uptake and elevated glucose transporter type 3 (GLUT3) expression, while glucose transporter type 1 (GLUT1) expression decreased in response to testosterone compared to healthy controls[23].

In type 2 diabetic rats, Sertoli cells also showed reduced protein levels and activity of lactate dehydrogenase (LDH) and monocarboxylate transporter 4 (MCT4)[23]. Xu *et al* reported structural alterations in diabetic rats, including apical extensions of vimentin in Sertoli cells[24]. Additionally, Brodjonegoro's findings revealed that hyperglycemia significantly alters Sertoli cell metabolism by upregulating GLUT1, GLUT3, MCT4, and antioxidant defense proteins like nuclear factor erythroid 2-related factor 2 (Nrf2) and catalase (CAT)[25].

3.3. Effect of diabetes on epididymal functions

Diabetes-related damage to the epididymis impairs sperm maturation and storage by disrupting mitochondrial function, increasing oxidative stress, and causing autophagy dysregulation. Studies in streptozotocin (STZ)-induced diabetic rats showed reduced epithelial height, thickened fibromuscular layers, basal membrane shrinkage, and epithelial vacuolization in the epididymis[26,27]. Li *et al* reported damaged stereocilia, increased fatty vacuoles in caput and cauda epididymal ducts, along with interstitial proliferation and inflammatory cell infiltration[28]. Kotian *et al* further observed reduced epididymal diameter and weight in diabetic rats[29].

3.4. Effect of diabetes on sperm parameters

DM significantly impairs male reproductive health by reducing semen quality. Key alterations include decreased sperm concentration, motility, and semen volume, alongside increased sperm DNA fragmentation and apoptosis[11,27,30,31]. Structural changes such as mitochondrial vacuolization in spermatogonia, impaired spermatogenesis, and reduced epididymal sperm count

have been reported in diabetic rats[10]. Epigenetic modifications, including altered cytosine methylation and abnormal lncRNA/mRNA expression, further disrupt spermatogenic processes[32–34]. Clinical findings in diabetic patients show lower ejaculate volume, motility, and DNA integrity compared to non-diabetics[35]. Elevated seminal interleukin-17 (IL-17) and interleukin-18 (IL-18) levels are also associated with poor semen parameters and may contribute to infertility[36].

3.5. Effect of diabetes on accessory glands

Experimental studies have demonstrated that DM induces significant structural damage, impairs secretory function, and reduces the weight of male accessory glands in rodents[37]. Among these, the seminal vesicles are particularly affected, with diabetes leading to reduced secretions largely due to oxidative stress-induced cell death[38]. Tsounapi *et al* reported marked atrophy and decreased weight of seminal vesicles in diabetic rats, impairing their contractile function and limiting seminal fluid production[12].

Clinical evidence also links T2DM with prostate enlargement and worsening of lower urinary tract symptoms[39]. In diabetic conditions, the prostate shows increased apoptosis, reduced mast cell count, decreased epithelial height, and diminished androgen receptor expression, all contributing to compromised prostate function[40].

3.6. Effect of diabetes on erectile function

Erectile dysfunction (ED), defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance, significantly affects a man's self-esteem and personal relationships. Diabetic men are approximately 3.5 times more likely to develop ED than non-diabetics, underscoring a strong link between the two conditions[41,42]. The erection process relies on the relaxation of smooth muscle in the cavernous tissue, primarily mediated by nitric oxide. Nitric oxide activates soluble guanylate cyclase, increasing cyclic guanosine monophosphate (cGMP) levels, which reduce intracellular calcium (Ca^{2+}), leading to smooth muscle relaxation and enhanced blood flow in the penis[43,44].

Studies show high prevalence of ED among diabetic patients. Hylmarova *et al* reported ED (IIEF-5 ≤ 21) in 28.1% of diabetic men, with better outcomes in those without nephropathy ($P=0.008$), and noted retrograde ejaculation in 8.8%[45]. Another study found that 71.1% of diabetic patients had ED, with 58.3% experiencing moderate to severe forms, linked to factors such as prolonged diabetes duration, poor glycemic control, autonomic neuropathy, and peripheral arterial disease[46].

3.7. Effect of diabetes on ejaculatory function

Ejaculatory dysfunction (EjD) refers to any condition where

normal ejaculation is disrupted, encompassing issues like premature ejaculation (PE), delayed ejaculation, painful ejaculation, reduced ejaculatory force, or complete absence of ejaculation. Research indicates that EjD is more prevalent, severe, and progressive in diabetic men compared to non-diabetics[45,47,48].

Corona *et al* found that among newly diagnosed type 2 diabetic men, 19.4% had moderate ED, 28.3% reported low sexual desire, 32.9% experienced delayed ejaculation, and 58.4% had PE[41]. Another large-scale study involving over 600 diabetic patients revealed that individuals with more than 10 years of diabetes were nearly three times more likely to suffer from PE than those with less than five years of disease duration[49]. Furthermore, a randomized controlled trial showed that retrograde ejaculation was more common in men with long-standing type 1 or type 2 diabetes, suggesting a strong link between diabetes duration and EjD severity[50].

4. Possible mechanism of diabetes-induced male reproductive impairments

Chronic diabetes exerts both structural and functional impacts on the reproductive organs. Numerous pathogenic mechanisms contribute to diabetic-related reproductive issues, including insulin deficiency, insulin resistance, elevated oxidative stress, disruptions to the hypothalamic-pituitary-testicular axis, germ cell apoptosis, endoplasmic reticulum stress, mitochondrial dysfunction, epigenetic modifications, chronic inflammation, germ cell autophagy, and metabolic imbalances. These factors may exert direct or indirect influences on reproductive health[9,11,97].

4.1. Insulin deficiency

Insulin, an anabolic polypeptide hormone produced by pancreatic β -cells in response to elevated blood glucose, plays a pivotal role in modulating the HPGA, thereby influencing reproductive health in both sexes. It affects gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) secretion, contributing to reproductive dysfunction in diabetic conditions, and also exerts direct effects on reproductive cells[98,99].

Beyond pancreatic production, insulin and its receptors are expressed in the testes (Leydig, Sertoli, and sperm cells) and brain[100–102]. Disruption of brain insulin receptors in mice leads to hypothalamic hypogonadism, diet-sensitive obesity, impaired spermatogenesis, reduced Leydig cell size, lower LH levels, delayed puberty, and subfertility[103]. The presence of insulin, insulin-like growth factor (IGF), LH, and FSH receptors, along with glucose transporters (GLUT-1, GLUT-4, GLUT-8) in testicular cells, supports insulin's direct role in testicular function[104].

Insulin contributes to testosterone synthesis by modulating LH receptor expression and maintaining healthy Leydig cell

populations[105]. Diabetes-induced insulin deficiency reduces Leydig cell count, testosterone levels, and alters testicular structure (weight, density, seminiferous tubule diameter)[106]. In Sertoli cells, insulin rapidly depolarizes the membrane, increasing Ca^{2+} uptake[107], while in sperm, receptors in the midpiece, acrosome, and membrane suggest cytological targets for insulin action[105].

4.2. Insulin resistance (IR)

IR is a major contributing defining feature and cause of T2DM[108]. There exists a correlation between IR and reproductive hormones: hormonal levels may influence insulin susceptibility, while sex hormones can help in improving this condition and reduce the progression of diabetes. Diabetes is highly co-related with androgens[109]. Testosterone levels are markedly reduced in individuals with diabetes compared to those without the condition, and lower testosterone levels correlate with a higher risk of diabetes development. IR serves as critical link between testosterone levels and diabetes. A decline in androgen levels contributes IR and DM. Multiple studies have reported that diabetic patients exhibit significantly reduced levels of testosterone (total), free testosterone, and sex hormone-binding globulin (SHBG) compared to non-diabetic individuals, while testosterone and SHBG being inversely related to IR[110,111]. Testosterone helps mitigate IR by promoting glucose uptake, reducing inflammation, enhancing mitochondrial activity, and limiting the proliferation of fat cells and tissues. This underscores the essential role of testosterone in regulating insulin sensitivity. Additionally, zinc-alpha-2-glycoprotein (ZAG), a newly recognized adipokine, has been identified as having crucial role in reducing IR. ZAG enhances insulin signaling pathways and influences the expression of adipokines and factors involved in inflammation. Research suggests that IR may negatively impact male fertility, particularly as part of metabolic syndrome (MetS), due to elevated insulin levels and disturbed glucose uptake seen in diabetes[68]. One study found that hypogonadism with type 2 diabetic individuals is strongly linked to increased IR, as evidenced by reduction in glucose infusion rates (GIR)[76].

4.3. Oxidative stress

Oxidative stress is a major cause of testicular dysfunction, contributing to male hypogonadism and infertility. In diabetes, inflammation and elevated oxidative stress reduce sperm vitality and increase DNA fragmentation[85].

Nrf2 is pivotal in mitigating oxidative and electrophilic stress by modulating intracellular antioxidant responses. In diabetes, down-regulation of the *Nrf2* gene within the testes significantly compromises oxidative defense[112]. Key antioxidants regulated by Nrf2, such as SOD, CAT, GSH-Px, play a vital role in neutralizing excessive oxidants and inhibiting harmful reactive oxygen species (ROS) production through the antioxidant response element (ARE)-dependent pathway[113,114].

Impaired signaling of Nrf2 has been linked to defective spermatogenesis[115]. Mentioned studies highlight the crucial role of Nrf2 in protecting spermatogenesis from oxidative damage. Elevated blood glucose levels lead to elevated ROS, which can severely impair the phosphoinositide 3-kinase/protein kinase B (PI3/AKT) signaling pathway. This, in turn, suppresses the mammalian target of rapamycin (mTOR) pathway & triggers abnormal autophagy in cells of testes[116]. While mild autophagy protects against testicular injury caused by high blood glucose levels[117], overactive autophagy activates the degradation of P62 (an autophagy related protein), further inhibiting the activation of Nrf2. This disrupts the P62-Nrf2 feedback loop, weakening the testis' antioxidant defenses and worsening oxidative stress, thereby creating a harmful cycle[118] (Figure 1).

4.4. Endocrine imbalance—disruption of HPG-axis

Sperm production is controlled by the HPGA, and disruptions in this axis can result in impaired spermatogenesis. Insulin promotes the GnRH production and release from hypothalamus, supporting activity of the HPGA[119]. *In vitro*, insulin also enhances the luteinizing hormone-releasing hormone (LHRH) derived release of gonadotropins. However, hyperglycemia disrupts GnRH secretion, leading to reduced levels of gonadotropins and prolactin (PRL), which decreases testosterone production by Leydig cells and results in impaired spermatogenesis. Diabetes-induced damage to Sertoli and Leydig cells reduces testosterone secretion, causing rise in FSH and LH due to negative feedback within the HPGA[10]. The development of infertility among men and sexual abnormalities are linked to disturbed HPGA function and are associated with impaired insulin (INS) signaling and altered kisspeptin expression in the hypothalamus. The interaction of kisspeptin with its receptor, G-protein-coupled receptor 54 (GPR54), activates GnRH neurons in the hypothalamus, triggers HPGA axis and stimulates gonadotropin hormones release. A complex named kisspeptin/GPR54 plays a crucial role in maintaining HPGA function and regulating GnRH secretion[10,120]. Kisspeptin also acts as "molecular switch" to initiate adolescence, as well as mutations in its gene can result in hypogonadotropic hypogonadism (HH). Lack of insulin leads in the reduction of hypothalamus kissprotein levels, which in turn lowers gonadal hormone secretion, resulting in hypogonadotropic hypogonadism. Research on Gnv-3 cell range, which consists of hypothalamic neurons expressing gonadal releasing hormones, has demonstrated that these neurons have INS receptors and are INS-sensitive[121]. Increased kisspeptin expression in hypothalamus preoptic region suggests insulin influences on kisspeptin levels in the Gnv-3 cells, with the mTOR pathway playing in maintaining the transcription of kisspeptin gene and production of mRNA. GnRH expression in brain and spinal cord is modulated through mTOR pathway, and its expression

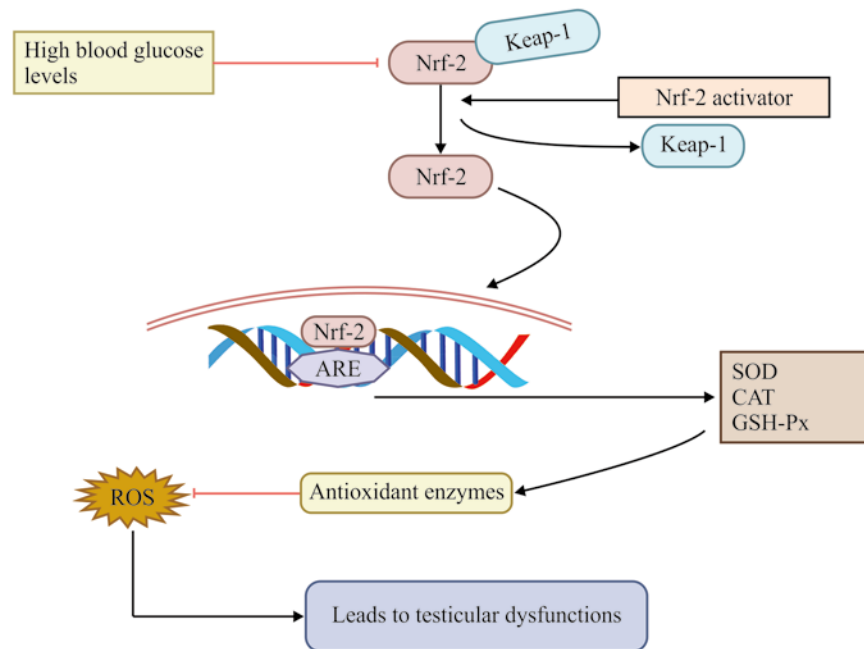


Figure 1. Diagrammatic representation of the relationship between diabetes-mediated oxidative stress. Nrf-2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element; ROS: reactive oxygen species; SOD: superoxide dismutase; CAT: catalase; GSH-Px: glutathione peroxidase.

boosts kisspeptin action, leading to enhanced LH secretion[111]. A study found that HH in type 2 diabetes patients is related to a notable rise in IR, as evidenced by reduction (36%) in the GIR[76].

4.5. Germ cell apoptosis

Apoptosis is a key factor contributing to male reproductive damage in diabetes, leading to degeneration and cell death in testicular and other reproductive tissues[122]. In healthy testes, apoptosis helps maintain sperm quality and quantity by removing damaged or abnormal germ cells. However, when apoptosis is dysregulated or occurs excessively, it results in the death of testicular cells, impairing spermatogenesis and causing infertility[123].

Diabetes-related germ cell apoptosis involves two primary pathways that contribute to reproductive abnormalities: first one, the extrinsic death receptor pathway and second one, the intrinsic mitochondrial pathway. These pathways can influence each other, with molecules from one affecting the other. The intrinsic pathway begins in the mitochondria, where high levels of ROS damage the outer and inner mitochondrial membranes, causing the release of cytochrome c into the cytoplasm. This release triggers apoptosome formation, a system made up of apoptotic protease activation factor-1 (Apaf-1), ATP and procaspase-9[124]. The apoptosome facilitates the auto-activation of procaspase-9, leading to the subsequent activation of procaspase-3[125]. The extrinsic signaling pathway initiates apoptosis through interactions mediated by membrane receptors. Certain death receptors from the tumour necrosis factor (TNF) receptor superfamily are involved

in this process. These receptors have an intracellular domain that is around 80 amino acids long and is referred to as the "death domain"[126]. Their extracellular sections also have cysteine-rich areas. The transmission of apoptotic stimuli from the cell membrane to intracellular signaling pathways depends on this domain. Other mechanism which involves the cell surface protein -Fas and is not depend on ROS, can also cause sperm apoptosis. Research has indicated that a greater proportion of Fas-positive spermatozoa is frequently seen in samples with lower sperm counts. Ligands such as TNF-alpha/TNFR1, Apo2L/DR4, Apo3L/DR3 & Apo2L/DR5 & their accompanying death receptors have been investigated the most. Since TNF-alpha plays a major role in insulin resistance, these interactions are also important in the development of additional diabetes problems[127].

Germ cells are particularly vulnerable to diabetes-induced cell death due to their sensitivity to this condition. In diabetic mice, insulin treatment three days after STZ administration helped to reduce overall glucose levels and prevented testicular cell apoptosis[128]. The Bcl-2 family of proteins regulates the processes involved in mitochondrial apoptosis. The tumour suppressor gene p53 has a major impact on how these proteins are regulated. This finding indicates a connection between hyperglycemia and germ cell death in diabetic mice[11](Figure 2).

4.6. Endoplasmic reticulum (ER) stress

ER stress may contribute to impairment in the male reproductive functions, affecting the testes, the epididymis, germ cells including sperms. Research has demonstrated that diabetes can cause ER

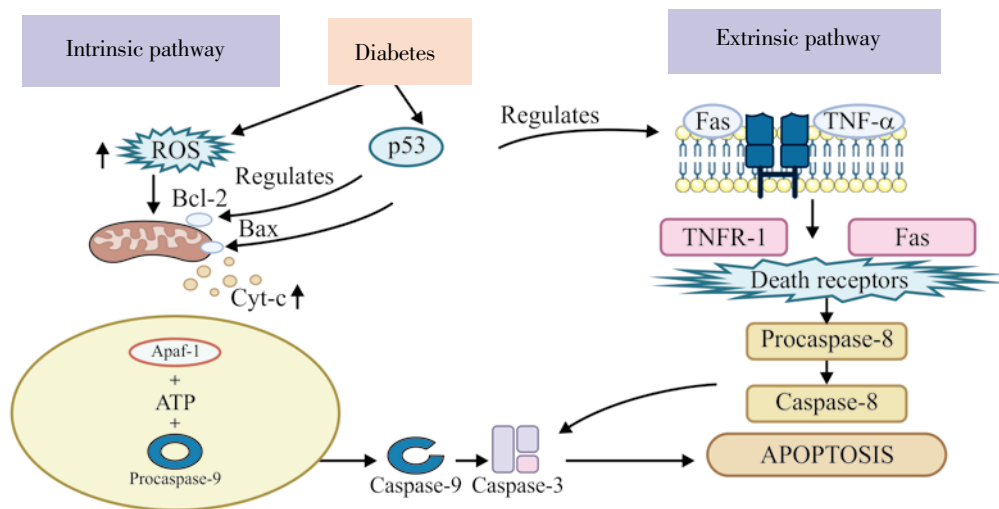


Figure 2. Schematic representation of apoptosis events. ATP: adenosine triphosphate; ROS: reactive oxygen species; TNF: tumour necrosis factor.

stress through oxidative stress pathways as well as by generating hyperglycemia in a diabetic rat model caused by STZ. Non-esterified fatty acids (NEFA), advanced glycation end products (AGEs), and an abundance of different nutrients are the outcomes of this situation, and they can all directly contribute to ER stress[129].

Research has indicated that ER stress may be a crucial signaling mechanism controlling apoptosis process in the germ cells, with male infertility potentially resulting from disruptions in ER strain[130]. Research on male fruit flies found high expression of ER stress-related genes in the male accessory gland, which led to significant ER stress and reduced fertility[131]. Stress of ER activates the unfolded protein response (UPR), also if UPR activity surpasses a certain threshold level, it causes cellular deterioration and finally induces predetermined cell death[132]. In the metagenomic animals, the UPR is triggered by three sensor proteins located on the membrane of ER: inositol-requiring kinase-1 (IRE1), activating transcription factor-6 (ATF6) and pancreatic eukaryotic translation initiation factor 2 α kinase (PERK)[133]. Chaperone protein BiP/GRP78 of ER binds with these mentioned sensor proteins, inhibiting their activation under normal conditions[15]. According to the competitive binding model of UPR initiation, misfolded or unfolded proteins in the ER compete with BiP/GRP78 for binding to the sensors, thereby activating these pathways and triggering downstream signaling processes[134] (Figure 3).

4.7. Mitochondrial dysfunctions

Current year highlights the critical role of mitochondrial health in male fertility. Mitochondria, as key energy producers, play a central part in regulating sperm production and influencing the growth of sperms, specialization, and programmed germ cells death in the testes[135]. Mitochondria also engaged in various activities

of cells like respiration of cell, metabolism, proliferation of cells, programmed cell death as well as production of reactive oxygen species. Any dysfunctions in the mitochondria leads to enhanced production of the ROS[97]. Diabetes-induced mitochondrial damage can lead to structural changes, altered membrane potential, and reduced energy output, thereby negatively impacting sperm production, movement, and the fertilization process[136]. Emerging evidence suggests that inositol may offer protective effects against these mitochondrial injuries[137]. Furthermore, abnormalities of mitochondria can disturb the apoptotic pathway (intrinsic) regulated by signals from mitochondria, thereby impairing the regulation of programmed cell death in undifferentiated germ cells. This disruption may result in unusual germ cells migration to the gonads, potentially disrupting the reproductive function of male[138].

Studies using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) and long-range PCR techniques to identify mutations in mitochondrial genome in infertile men revealed that deletions of 4977 and 7599 base pairs in mtDNA are linked to sperm production failure[139]. Mitochondria also have a key role in the metabolism of numerous proteins related to sperm function. Comparative analyses of the proteomes of sperm from diabetic and non-diabetic men have revealed appropriate variations in proteins critical for sperm production and conception[140]. Approximately 50% of these protein anomalies can be attributed to mitochondrial metabolism disturbances. Analysis of protein interaction networks suggests that dipeptidyl peptidase-4 and cystatin-C levels reduction inside mitochondrial matrix may significantly contribute to the diminished sperm motility observed in patients with diabetes[31] (Figure 4).

4.8. Germ cell autophagy

Autophagy is essential for maintaining healthy testicular function, as lack of autophagy can lead to the degeneration of germ cells

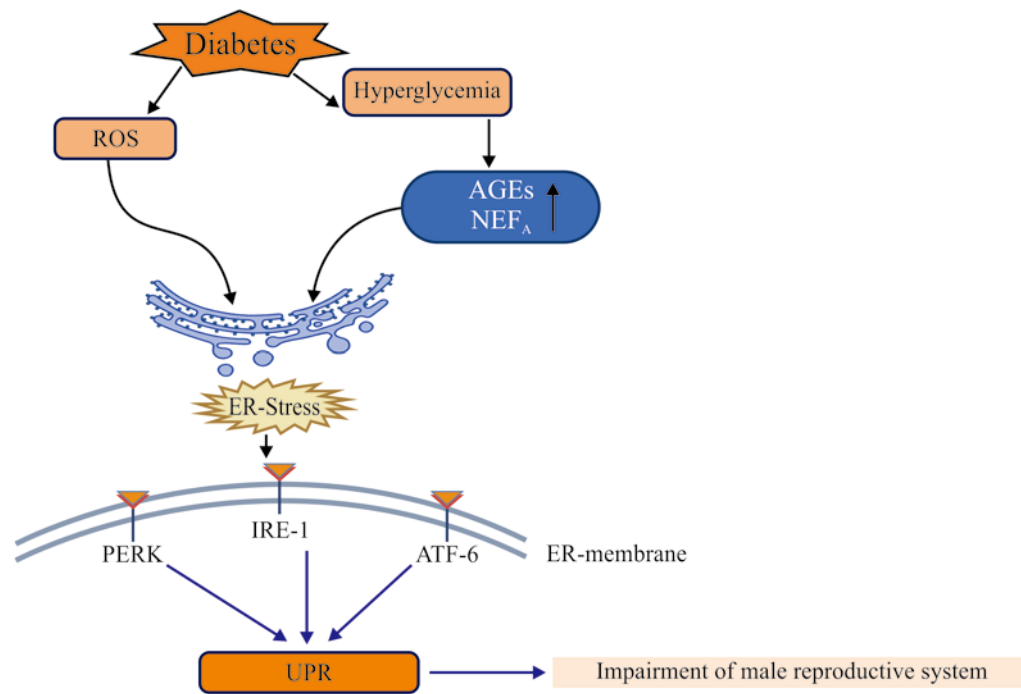


Figure 3. Diagrammatic representation of diabetes-induced endoplasmic reticulum (ER)-stress. ROS: reactive oxygen species; AGEs: advanced glycation end-products; NEFA: non-esterified fatty acids; PERK: pancreatic eukaryotic translation initiation factor 2 α kinase; IRE-1: inositol-requiring kinase-1; ATF-6: activating transcription factor-6; UPR: unfolded protein response.

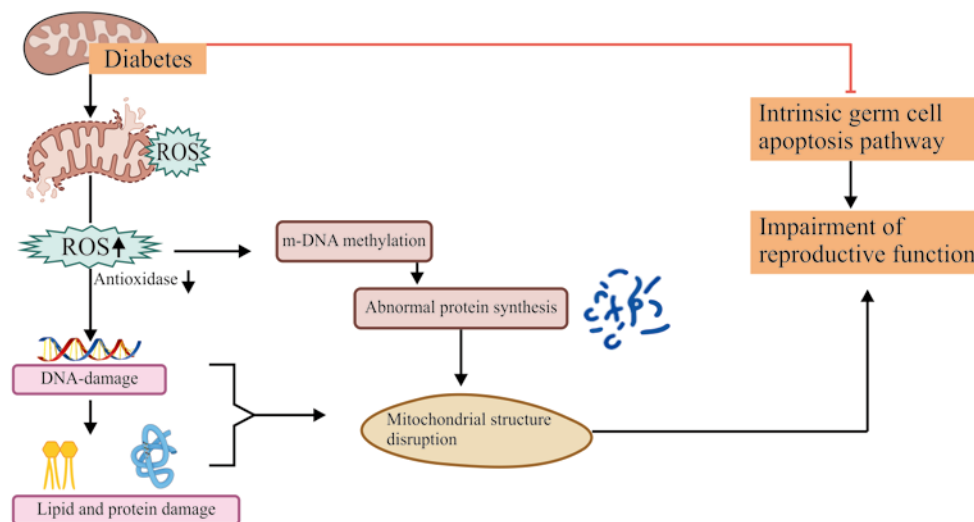


Figure 4. Diagrammatic representation of diabetes-induced mitochondrial dysfunctions. ROS: reactive oxygen species.

and disrupt cells internal balance by breaking down and recycling of components like mitochondria and the ER[117]. Studies on animals indicate that in the initial phases, oxidative or ER stress can prompt a compensatory increase in autophagy, which helps maintain cellular homeostasis by removing harmful substances such as misfolded proteins in the ER, ROS-induced cytosolic proteins damage, and malfunctioning in mitochondria and ER. The mammalian counterpart of yeast autophagy-related genes (Atg), that is, the unc-51-like kinase (Ulk1) complex, controls the initiation of autophagy. Ulk1, a Ser/Thr protein kinase, Atg13, and FIP200, the mammalian counterpart of yeast Atg17, are all part of this complex. The transformation of microtubule-associated

protein-1 light chain 3B (LC3B) from LC3- I to LC3- II is a crucial stage in the creation of autophagosomes. This change is brought about by the autophagy-related proteins Atg3 and Atg7, also by the Atg12-Atg5-Atg16L complex conjugating LC3- I to produce the lipidated LC3- II form. Autophagy is induced when cells undergo nutritional deprivation to replenish missing components. Levels of LC3- II serve as markers for presence of autophagosome. Later, autophagosome forms autolysosome after fusing with lysosome[11,141].

When cellular stress persists for long, sustained autophagy activation can ultimately lead to impairment in autophagy function[142]. Research has indicated that hyperactivity of

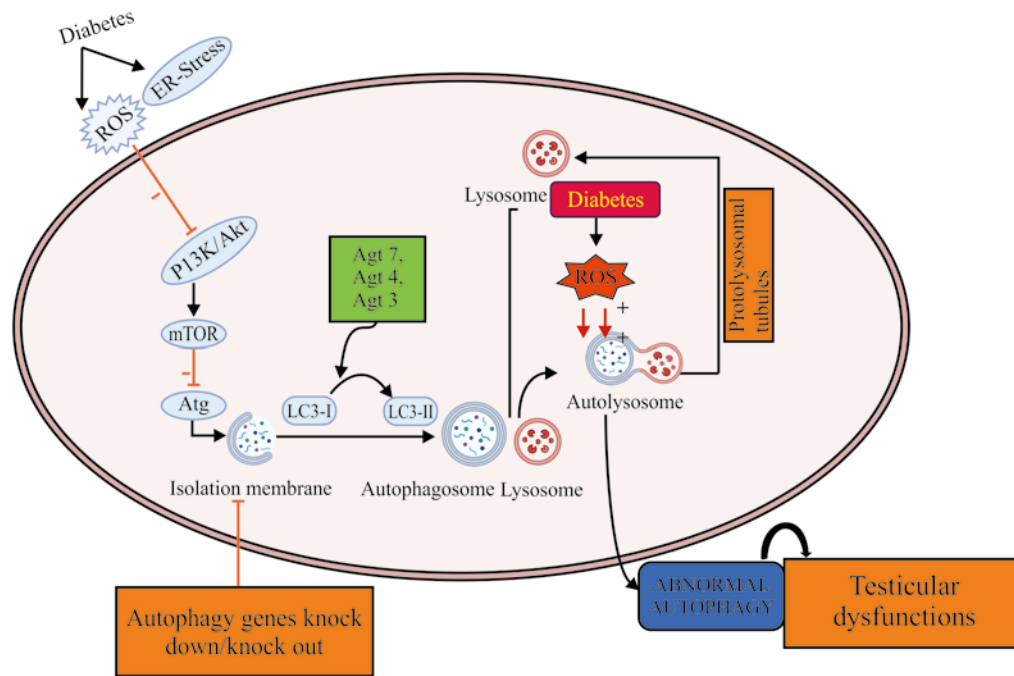


Figure 5. Diagrammatic representation of macroautophagy regulation and potential drug targets. ROS: reactive oxygen species; PI3K/Akt: phosphoinositide 3-kinase/protein kinase B; ER: endoplasmic reticulum; mTOR: mammalian target of rapamycin; Atg: autophagy-related genes; LC: light chain.

the mTOR signaling pathway in the seminiferous tubule epithelium[143], is a key factor contributing to germ cell and testicular issues damage in diabetes[117,144]. Evidence also suggests that suppressing the mTORC1 pathway offers protective against both type-1 and type-2 diabetes-induced reproductive damage (Figure 5).

4.9. Chronic inflammation

Ongoing inflammation can disrupt the hormonal functions of the testes and contribute to defects in male reproduction by provoking cytokine release or by directly or indirectly impacting the HPGA and affecting testicular cells[145]. Like, C-C motif chemokine ligand 2 (CCL2) and interleukin-1 beta (IL-1 β) reduce production of androgens by disrupting enzyme's function involved in steroidogenesis, finally leading to apoptosis of Leydig cells[103]. TNF- α stimulates molecule production like nitric oxide, which is crucial for maintaining inflammation but can adversely affect sperm formation, damage sperm cell membranes, and reduce quality of semen[146]. Studies indicate that the interplay between inflammation and diabetes exacerbates their combined negative effects on male reproductive health. The key mechanisms include an overproduction of ROS, excess cortisol release, triiodothyronine levels reduction, and disturbances in the statin/follistatin/activin axis[145].

5. Conclusion and future prospect

Diabetes is now a major global health problem, leading to many serious health issues, including a higher risk of complications and

death. One important but often overlooked effect of diabetes is its impact on male reproductive health. Research has shown that diabetes can affect male fertility through several pathways, such as hormonal changes, problems with glucose transport, increased oxidative stress, harmful glycation products, and mitochondrial dysfunction. This review has discussed these factors to better understand how diabetes harms male reproductive functions. While the connection between diabetes and male infertility is gaining attention, there are still many gaps in our understanding. More large-scale human studies are needed to confirm existing findings and to identify clear markers that can help in early diagnosis. Future research should also explore new treatments that target oxidative stress, hormonal imbalances, and mitochondrial health. With advances in science, there is hope for developing better ways to prevent and treat reproductive problems in diabetic men. Incorporating reproductive health as an essential component of regular diabetes care could significantly improve the overall quality of life for affected individuals.

Conflict of interest statement

The authors declare no conflicts of interest to disclose.

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Authors' contributions

Tanvi Jangid contributed to the original draft preparation and was involved in review and editing. Aditya Jain was responsible for conceptualization and also contributed to review and editing. Gauri Shankar Bhardwaj contributed to the review process and figure editing. Ram Niwas Jangir was involved in editing, original draft writing, and visualization. Gyan Chand Jain contributed to the review and editing of the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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