



# Abnormalities in sex hormones and sexual dysfunction in males with diabetes mellitus: A mechanistic insight

Nida Andlib<sup>a,b</sup>, Mohd Sajad<sup>a,b</sup>, Rajesh Kumar<sup>b</sup>, Sonu Chand Thakur<sup>a,\*</sup>

<sup>a</sup> Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi 110025, India

<sup>b</sup> Department of Reproductive Biomedicine, The National Institute of Health, and Family Welfare, Baba Gang Nath Marg, Munirka, New Delhi 110067, India

## ARTICLE INFO

### Keywords:

Diabetes mellitus  
Hyperglycemia  
Infertility  
Oxidative stress  
Erectile dysfunction

## ABSTRACT

Diabetes is a considerable metabolic disorder that can lead to a series of complications, involving the malfunctioning of the reproductive system of males. It has been observed that there is a gradual rise in male diabetic patients and almost half of the diabetic males have low semen quality and decrease reproductive function. In diabetic conditions, prolonged hyperglycemia leads to oxidative stress, diabetic neuropathy, and insulin resistance. Insulin resistance and its deficiency can impair the hypothalamus, pituitary gland, gonads, and perigonads. This causes a decrease in the secretion of gonadal steroids such as GnRH (gonadotropin-releasing hormone), FSH (follicle-stimulating hormone), LH (luteinizing hormone), and Testosterone. Moreover, it also causes damage to the testicles, spermatogenic and stromal cells, seminiferous tubules, and various structural injuries to male reproductive organs. During spermatogenesis, glucose metabolism plays an important role, because the fundamental activities of cells and their specific features, such as motility and mature sperm fertilization activity, are maintained by glucose metabolism. All these activities can influence the fertility and reproductive health of males. But the glucose metabolism is primarily disrupted in diabetic conditions. Until now, there has been no medicine focusing on the reproductive health of diabetic people. In this chapter, we review the consequences of diabetes on the reproductive system of males and all the pathways involved in the dysfunction of the reproductive system. This will help interpret the effects of DM on male reproductive health.

## 1. Introduction

Diabetes mellitus (DM) is an incurable disorder with varied morbid potential and causes damage to various organs. According to an IDF report, there are 463 million adults suffered from DM worldwide, which is supposed to rise to 578 million by 2030. Hyperglycemia is the most common symptom of diabetes, which is caused either by an autoimmune disease of pancreatic cells, that leads to a drop in insulin secretion in type 1 diabetes (T1DM) or by complete resistance or poor insulin secretion in type 2 diabetes (T2DM). In the past few decades, awareness and knowledge are very limited about diabetes and its effects on reproductive health. The main target of medicinal treatment was to eliminate the cause of disease to restore normal health. However, it is very essential to observe the consequences of DM on reproductive function. It causes impairment in both the male and female reproductive systems (Baccetti et al., 2002; Seethalakshmi et al., 1987; Sajad and Thakur, ), leads to a reduction in the fertility ratio, and reproductive casualties rise (Greene, 1993; Lucas et al., 1989; Meller et al., 1981;

Mills et al., 1988). Endothelial dysfunction, vascular dysfunction, and resulting oxidative stress are often caused by diabetes (Brownlee, 2001, 2005; Abdul-Ghani et al., 2006), and it is not unusual if it directly or indirectly affects several activities of the reproductive system (Dinulovic and Radonjic, 1990; Glenn et al., 2003; Hassan et al., 1993; Jackson, 2004; Mallidis et al., 2011; Sajad et al.). It is shown that almost half of DM men have poor semen quality and dysfunctional reproductive systems. In diabetic men, reproductive activity is affected at several steps because of endocrine control of spermatogenesis itself, or by impairing penile erection and ejaculation (Sexton and Jarrow, 1997; Baccetti et al., 2002; Ballester et al., 2004; Daubresse et al., 1978; Dinulovic and Radonjic, 1990; Garcia-Diez et al., 1991; Handelsman et al., 1985). It is affected by various mechanisms like neuropathy, a rise in oxidative stress, and endocrinopathies. There is a substantial body of literature on these reports, but their findings have been contradictory, as the described malfunctions are unlikely to cause significant impairment in reproductive function alone (Sexton and Jarrow, 1997). However, diabetes mellitus is a known source of sexual dysfunction in men, which

\* Corresponding author.

E-mail address: [sthakur@jmi.ac.in](mailto:sthakur@jmi.ac.in) (S.C. Thakur).

<https://doi.org/10.1016/j.acthis.2022.151974>

Received 2 August 2022; Received in revised form 7 November 2022; Accepted 10 November 2022

Available online 28 November 2022

0065-1281/© 2022 Elsevier GmbH. All rights reserved.

may result in subfertility.

## 2. Effect of DM on males

Sexual dysfunction caused by DM has been broadly studied in males. There are various data showing clinical and experimental studies on diabetic males. There are four stages in which DM affects the male reproductive system, which involves structural changes in reproductive organs, erectile dysfunction, malfunctioning in ejaculation, and changes in semen quality. According to various reports, erectile dysfunction (ED) is caused in 59 % of men affected by DM. Many diabetic patients who are impotent (DMED) have nerve stiffening in the penis or pearly neuropathy. Due to DM, testosterone level also decreases which affects vascular endothelial function. ED is caused by hyperglycemia as it causes an increase in the quantity of ROS (reactive oxygen species) and AGEs (advanced glycation end products), eNOS (endothelial nitric oxide synthase) metabolism is inhibited and reduction in synthesis of endothelial and nitric oxide (NO) discharge (Fig. 1).

Most of the research has shown that diabetic males have erectile dysfunction. Their testosterone level is also reduced which affects the activity of endothelium. In penile erection, NO is a principal neurotransmitter (Sajad and Thakur, 2020). In DM males, hyperglycemia produces more ROS and AGEs but hinders the metabolism of eNOS which leads to the decline of synthesis and release of NO in endothelial. The pelvic sympathetic nerve fiber synchronizes the process of ejaculation. Impairment in it may be caused by peripheral neuropathy which leads to irregular contraction of the external urethral sphincter, causing retrograde ejaculation. As we know diabetes causes structural as well as functional modification in reproductive organs, Doppler detected decreased velocity in testicular blood flow in diabetic rats (Zhao et al., 2020). A reduction in VEGF (vascular endothelial growth factor)

expression may hinder the functioning of vascular endothelial cells which leads to a disturbance in microcirculation in testis which in turn causes morphological and structural modification. It is believed that in immature rats, DM can cause a gonadal developmental setback, sexual behavior and testosterone synthesis are lowered while promoting atrophy of gonads.

DM degrades sperm viscosity, motility and intensifies sperm DNA fragmentation and cell death (He et al., 2021; Imani et al., 2021; Mar-esch et al., 2018) (Fig. 1). NO inhibits superoxide anion and damage caused by lipid peroxide to sperm membrane. It also steadies membranes of cells and lysosomes; cGMP rises in sperm and initiates activation and capacitation of sperm (Sajad and Thakur, 2020). It affects spermatogenesis by keeping a check on motility and lipid peroxidation of sperm. As a vasoconstrictor peptide, endothelin (ET) is necessary for sperm maturation. Both ET and NO manage the secretion of male reproductive hormones and spermatogenesis. The secretion of ET can be inhibited by NO. According to a study, levels of ET increases while NO decreases in diabetic patients, leading to endothelial function damage (Shi et al., 2017).

Several clinical and experimental research have recommended that diabetes affects men's reproductive system at three levels, specifically pretesticular (Suresh and Prakash, 2012), testicular (Ghosh et al., 2014) and post-testicular levels (De Young et al., 2004) (Table 1).

### 2.1. Pre-testicular effect of DM

The hypothalamus-pituitary-gonadal (HPG) axis is disrupted in DM which leads to alteration in the expression of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone in men. In T1DM, the HPG axis is significantly suppressed by DM and thus decreases Follicle-stimulating hormone and luteinizing hormone feedback

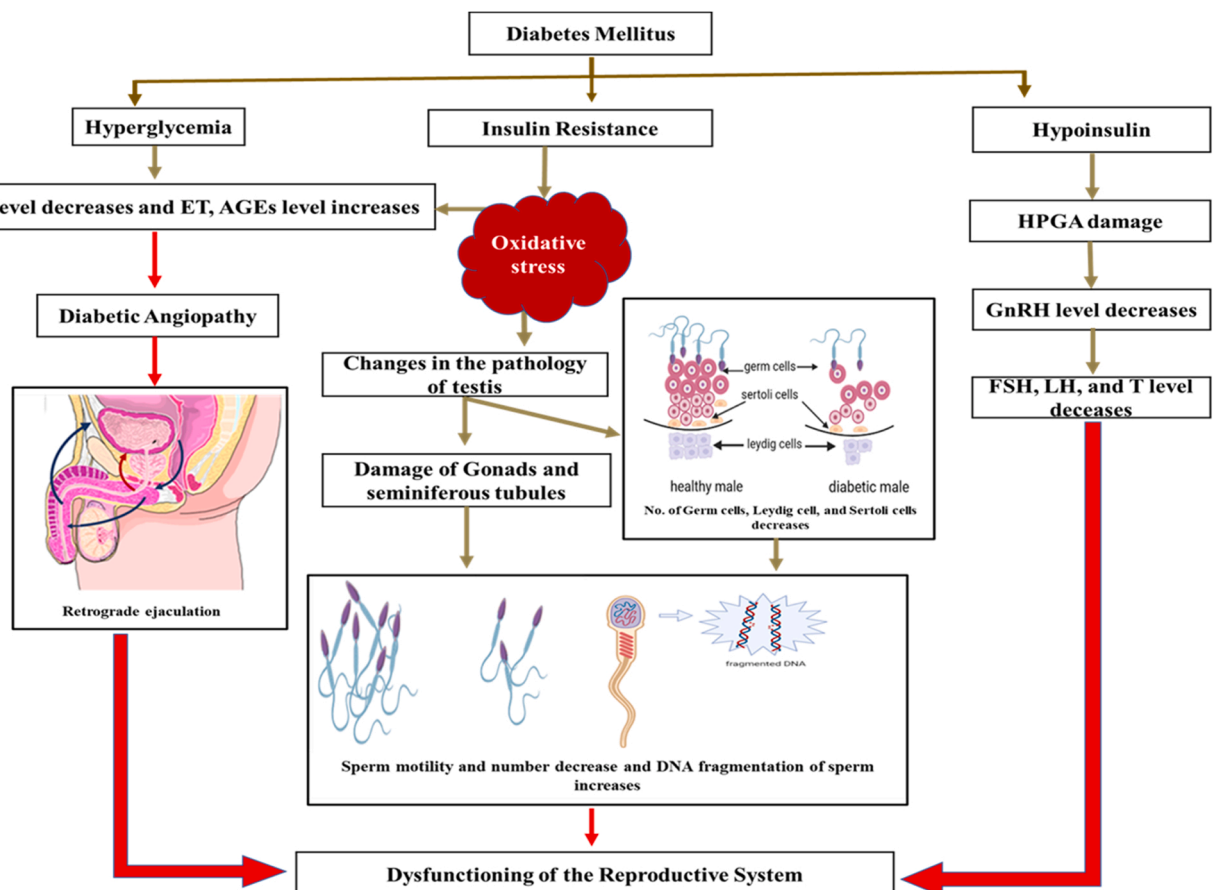


Fig. 1. Impact of diabetes mellitus on male reproductive function.

**Table 1**  
Effects of DM on different levels of the reproductive system of males.

Pre-testicular effect	Testicular effect	Post-testicular effect
FSH and LH level decreases	ROS increases in testis	Erectile dysfunction
Leydig cell function decreases	Antioxidant enzymes decreases	Abnormal sexual behavior
Steroidogenesis decreases	Sperm nuclear and mitochondrial DNA fragmentation increases	
	Abnormal cell apoptosis	
	Sperm count, motility, and viability decrease	
	No. of abnormal spermatozoa increases	

to extrinsic GnRH (gonadotropin-releasing hormone) (Erol et al., 2002). In T2DM persons, the decline in function of Leydig cells is reported due to limited secretion of testosterone (Pitteloud et al., 2005). It is reported that in DM animal models like STZ (Kanter et al., 2013; Mohasseb et al., 2011), alloxan (Ghissi et al., 2012; Hafez, 2010) and nicotinamide+ STZ (Ahangarpour et al., 2015), and in BB rats (Cameron et al., 1990), there is a decline in the concentration of reproductive hormones (testosterone, FSH and LH). Various studies have indicated that the consequence of diabetes mellitus on the HPG axis isn't type-dependent, as T1DM and T2DM models show similar results.

## 2.2. Testicular effect of DM

### 2.2.1. Metabolism of energy in the testis

In testicular energy metabolism, Sertoli cells or nurse cells are significantly involved which are among vital elements of the blood-testis barrier. In germ cells, lactate is the principal component of energy (ATP) production in testicular energy metabolism (Hafez, 2010). Various in vitro studies have reported that the removal of either insulin (Hafez, 2010) or glucose (Ghissi et al., 2012) from the media of cultured Sertoli cells leads to alteration of Sertoli cells to glucose transport as observed in modified expression of genes of GLUT1 and GLUT3 (glucose transport). But in vitro study in which insulin-deprived Sertoli cells (closely imitate T1DM) are used have reported declined glucose utilization even after an increase in gene expression of glucose transport (Hafez, 2010). Genes linked with metabolism and transport of lactate are down-regulated as reported in this study. Cultured Sertoli cells (acquired from T2DM rats) exposed to T, increase glucose utilization and overexpressed GLUT3, but under expressed GLUT1 gene expression assimilate with cultured Sertoli cells acquired from pre-diabetic rats. In cultured Sertoli cells (acquired from T2DM rats), there is also a reduction in the expression of protein of LDH (lactate dehydrogenase) and MCT4 (monocarboxylate transporter-4), in addition, to a decrease in lactate dehydrogenase activity (Rato et al., 2015). In STZ-induced T1DM animal models also, it is reported that testicular LDH activity reduces in DM (Kyathanahalli and Manjunath, 2014). This suggests that in both the T1 and T2DM patient's similar events can be seen.

### 2.2.2. Testicular oxidative stress

Antioxidant mechanism in testis confirms that the two principal incidents in the testis i.e., spermatogenesis and steroidogenesis aren't adversely altered by oxidative stress. These antioxidants which are present in the testis play an important role in reducing oxidative stress, which is presently evaluated as the principal source of testicular dysfunction concealing the pathological reaction of a vast variety of circumstances including diabetes mellitus. There is a remarkable decline in antioxidant enzymes and an elevation in testis lipid peroxidation, in both T1DM and T2DM animal models. Studies using STZ-induced T1DM rats have indicated a remarkable decline in antioxidant enzymes like SOD (superoxide dismutase), CAT (catalase) and GPx (glutathione peroxidase) activities, and a remarkable rise in MDA (malondialdehyde)

level (De Young et al., 2004; Pitteloud et al., 2005). In alloxan-induced T1DM rats studies, a remarkable decline in superoxide dismutase, glutathione peroxidase and catalase (antioxidant enzymes) activities and a remarkable rise in thio-barbituric acid-reactive substance quantity in the testis is reported (Ghissi et al., 2012). Whereas another study using STZ-induced T1DM rats indicated that there isn't any remarkable alteration in the testicular SOD, CAT, GPx and MDA (antioxidant enzymes) activities even after 1 and 8 weeks (Gobbo et al., 2015).

### 2.2.3. Steroidogenesis

Cholesterol is used in the synthesis of steroid hormones including testosterone. After testosterone formation, spermatogenesis is supported by the secretion of Leydig cells. In STZ- induced T1DM model there is a remarkable rise in the concentration of cholesterol in the testis (Sm and Mahaboob Basha, 2017). In another study, Streptozotocin-induced type-1 diabetes mellitus rat model testis, there is a remarkable decline in  $3\beta$ -hydroxysteroid dehydrogenase (HSD) and  $17\beta$ -HSD activities (Reddy et al., 2016). Besides this, in Streptozotocin-induced type-1 diabetes mellitus rats' testis, there is also a remarkable decline in StAR (steroidogenic acute regulatory protein) expression and CYP11A1 (the 1st enzymatic step in steroidogenesis). This rise in the concentration of testicular cholesterol (Sm and Mahaboob Basha, 2017) may be caused by suppression of the StAR (transporter of cholesterol), which leads to aggregation of cholesterol. These studies suggested that the decrease in T concentration in diabetes mellitus in between excessive concentration of cholesterol in testis may be due to suppression of StAR and marker enzymes ( $3\beta$ -HSD, CYP11A1 and  $17\beta$ -HSD) expressions.

### 2.2.4. Spermatogenesis

Various experimental (Reddy et al., 2016; Sangameswaran and Jayakar, 2008) and clinical (Delfino et al., 2007) studies have manifested the negative impact of DM on spermatogenesis and sperm associated parameters. STZ-induced T1DM animal model has exhibited a decline in daily production of sperm, sperm count and motility (Gonzales et al., 2013; Suresh and Prakash, 2012) and a rise in abnormal morphology spermatozoa percentage (Kanter et al., 2013). Alloxan-induced T1DM animal models (Ghissi et al., 2012; Hafez, 2010) also showed similar outcomes.

### 2.2.5. Testicular histology and germ cell apoptosis

Various studies on T1DM (Al-Roujeaie et al., 2017; Kanter et al., 2013) and T2DM (Long et al., 2015) animal models have shown a negative impact on the histology of testis. Oxidative stress is associated in the deformation of testis in DM animal models. Different degree of morphological distortion is reported in various animal models of T1DM like STZ (Al-Roujeaie et al., 2017; Kanter et al., 2013), alloxan (Hafez, 2010; Shalaby and Hamowieh, 2010) and BB (Cameron et al., 1990), compared to T2DM like STZ + high-fat diets model (Long et al., 2015). In STZ- induced T1DM model, mean Johnsen's score (evaluation of the degree of spermatogenesis) is remarkably low (Kanter et al., 2012, 2013). In DM, shrinkage of testicular have also been reported with a remarkable reduction in volume and diameter of the seminiferous tubules, and decline in Leydig and Sertoli cells number (Al-Roujeaie et al., 2017; Kanter et al., 2013). A remarkable decline in spermatogonia, spermatocytes and spermatids (germ cells) population has also been reported at various stages (Kanter et al., 2013). In diabetic rats, a rise in apoptotic germ cells number is observed which may be due to oxidative stress in DM. A study reported that in STZ induced diabetic rats' testis, there is increased activity of caspase-3 (Mohasseb et al., 2011). In T1DM (Ghosh et al., 2014) and T2DM (Long et al., 2015) rats, there is upregulation of the pro-apoptotic protein (Bax) and down-regulation of the anti-apoptotic protein (Bcl-2) while caspase 8 and 3 expression rise in T1DM rats (Jiang et al., 2013). Upregulation of p38 and p53 (pro-apoptotic genes) have also been reported in STZ induced T1DM rats (Fode et al., 2012). TUNEL staining technique also confirms the increase of apoptotic cells in various studies (Kanter et al., 2012, 2013). All these

studies concluded that in DM, there is a rise in the apoptotic germ cells population.

### 2.3. Post-testicular effect of DM

Abnormal sexual behavior is reported in DM animal models. Various studies have reported that there is a poor erectile function in DM as it lowers penile cGMP concentration, extends mount, intromission and ejaculatory latencies, and lower mount and intromission prevalence (Al-Roujeaie et al., 2017). The decline in sexual behavior is due to the reduction of testosterone secretion by Leydig cells (Delfino et al., 2007). Other studies reported that male diabetic rats have shown subfertility when copulated with female healthy rats (Reddy et al., 2016; Suresh and Prakash, 2012). There is also a rise in the loss percentage of pre and post-implantation and a decline in the figure of live fetuses (Reddy et al., 2016). Diabetes mellitus increases conception time due to poor sperm characteristics (Reddy et al., 2016) and doesn't affect the pregnancy rate.

#### 2.3.1. Erectile dysfunction (ED)

Any complication in erectile function eventually leads to infertility in males (Fode et al., 2012). Almost 35–75 % of DM males have ED (Kamdar and Shah, 2014). In diabetic males, ED pathophysiology is mainly affected by dysfunction in endothelial and neurological damage via the autonomic system (De Angelis et al., 2001; Gaunay et al., 2013). Besides these, ED is also affected by side effects of pharmacology and alteration in the endocrine. Erection is chiefly achieved by the relaxation of smooth muscles. In the case of diabetes, there is a defect in the smooth relaxation of blood vessels dependent on endothelium which affects the penis microvasculature and leads to arteriogenic and veno-occlusive ED types (Solomon et al., 2003). An increase in endothelium adhesion molecules expression (ICAM-1 and VCAM-1) and oxidative stress mediate this alteration (Gaunay et al., 2013). In DM, hyperglycemia causes a rise in AGEs (advanced glycation end products) which may lead to vascular dysfunction in the penis. This may lead to rise in hyperglycemia with deteriorating erectile function (Awad et al., 2010; Kamdar and Shah, 2014). The penis is sensitive to both micro vasculopathies and macro vasculopathies (Gaunay et al., 2013). Impaired penile circulation and atherosclerosis are caused by macrovascular disorders (Meller et al., 2013). End-stage renal disease and blindness are caused by microvascular disorders (). It is observed that ED is common in diabetic males with microvascular disorder (Vardi, 2009).

A normal erection is acquired by an integral neurological system. In DM, oxidative stress and hyperglycemia damage the direct nerve fiber and later changes in sensory and motor (Gaunay et al., 2013). Dysfunction in the autonomic nervous system is principally affected by a decline in parasympathetic input which leads to ED in diabetic men. For smooth muscle relation in the corpus cavernosum requires the involvement of parasympathetic nervous system (Gaunay et al., 2013; Hecht et al., 2001). Bladder dysfunction, retrograde ejaculation and other sexual dysfunctions are linked with autonomic neuropathy in diabetic men (Gaunay et al., 2013; Kamdar and Shah, 2014). Nitric oxide synthesis declines in diabetic neuropathy which is a principal element in the veno-occlusive cascades in erections. Erectile dysfunction in diabetic men is also caused by hormonal changes which are due to the malfunctioning of the HPG axis. Hypogonadotropic hypogonadism also leads to ED (Tripathy et al., 2003). In DM, ED is also caused by various drugs like antihypertensive drugs (beta-blockers and diuretics) (Kamdar and Shah, 2014). Whereas, psychotropic drugs like antipsychotics and selective serotonin reuptake inhibitors may increase difficulty in erection and also influence sexual activity (Kamdar and Shah, 2014).

#### 2.3.2. Ejaculatory disorders

It is the leading cause of infertility in diabetic men. Ejaculatory disorder comprises various dysfunction related to an ejaculation like delayed ejaculation, premature ejaculation, anejaculation, and

retrograde ejaculation (RE). Fertilization requires normal ejaculation. Anejaculation and RE are associated with DM and are more complicated for fertility than other ejaculatory diseases. About 10% diabetic men have anejaculation (Gaunay et al., 2013; Kamischke and Nieschlag, 2002). In DM, peristalsis of the vassal and seminal vesicle lining is prevented by autonomic dysfunction which blocks ejaculation to reach the urethra (Gaunay et al., 2013). Diabetic dysfunction in the autonomic contributes to RE pathophysiology. Almost 6% of young males affected with diabetes have ejaculatory diseases (Dinulovic and Radonjic, 1990). It has been reported that diabetic men have a higher rate of RE whereas nondiabetics have no RE cases (Fedder et al., 2013).

#### 2.3.3. Libido

In DM, the decline in libido is common (25 %) in males, and is mainly caused by defects in the HPG axis which leads to hypogonadotropic hypogonadism. It is mainly caused by the decline in testosterone level besides other sexual disorders. (Malavige et al., 2008). ED was also linked with premature ejaculation and libido. A decline in libido is a serious issue in context with fertility in diabetic men.

### 3. Effect of DM on glucose metabolism in sperm

In DM, lack of insulin generates effects on testicular function (Balester et al., 2004; Zhao et al., 2011). Glucose metabolism is important for in vivo preservation of spermatogenesis and the fertility capacity of sperm (Mancine et al., 1960; Zysk et al., 1975). Various simple sugars like glucose, fructose and mannose can be effectively used by sperm cells as a source of nutrients (Frenkel et al., 1973) and the energy production of spermatozoa needs catabolism of glucose to pyruvate and lactate by the glycolytic pathway enzymes. Sertoli cells (SCs) produce lactate to preserve germ cell survival and the endocrine system fundamentally controls this process by sex steroid hormones (Boussouar and Benahmed, 2004; Meller et al., 2013; Oliveira et al., 2012, 2011), FSH (follicle-stimulating hormone) and insulin (Malavige et al., 2008). When the ability of spermatozoa is modified to use the substrates which are associated with ATP production then it compromises with the sperm motility and in consequence also affect its fertility ability (Klip et al., 1994). Spermatogenesis maintenance involves lactate production by the Sertoli cells from glucose. As a result, blood to germ cell transfer of glucose and other metabolic intermediates is extremely governed in the basal to adluminal compartment, because of the existence of blood-testis-barrier (BTB) (Bucci et al., 2011; Riera et al., 2009). Glucose transporters (GLUTs), a specific carrier, that spermatozoa need to reconcile the uptake of glucose from the surrounding medium into the cells (Handberg et al., 1990; Hecht et al., 2001). It is also present in mature sperm cells, as they require it to sustain basic functions of cells, besides specific activity, including fertilization ability and motility (Ullisse et al., 1992) (Table 2). Depletion of GLUTs has been associated with diabetes (Burant and Davidson, 1994). Therefore, diabetic patients have an inability to transport glucose, which confers with the results supporting this disease association with disruptions in sperm metabolism, which leads to subfertility or even infertility. As we already know the expression of Glut1, Glut2, Glut3, Glut4, Glut8 has been experimentally proven to be present in the testis (Carosa et al., 2005; Galardo et al., 2008; Kokk et al., 2004; Nakayama et al., 2004; Verma and Haldar, 2016), with Glut1 and Glut3 showing a synergistic part in

**Table 2**  
Position of isoforms of glucose transporter (GLUT) in the different segments of the sperm.

Region of sperm	Glucose transporter isoforms
Acrosome	GLUT 1, GLUT 2, GLUT 8, GLUT 9b
Middle piece	GLUT 3, GLUT 5, GLUT 8, GLUT 9a, GLUT 9b
Principal piece	GLUT 1, GLUT 2, GLUT 5, GLUT 8, GLUT 9b
End piece	GLUT 1, GLUT 2



glucose retainment (Galardo et al., 2008; Verma and Haldar, 2016). In addition to facilitated glucose transport, Sertoli cells also help in glucose utilization and lactate fabrication, which is regulated by several hormones like FSH and testosterone (Oliveira et al., 2012; Pitetti et al., 2013; Rato et al., 2015; Skinner and Griswold, 1982). For the development and functioning of the testis, insulin family of growth factors [insulin, IGF1 (insulin-like growth factors I) and IGF2 and INSR (insulin receptors) in addition INS1R (type-I insulin-like growth factor receptor)] is necessary (Borland et al., 1984; Frenkel et al., 1973; Jutte et al., 1983). Leydig cells, Sertoli cells, spermatogonia and spermatocytes express IGF1 and INS1R. Sertoli cells' energy metabolism is regulated by the utilization of nucleotides (GTP, ATP, UTP), by the secretion of pyruvate, transferrin and lactate, it is concluded that insulin is highly participating in the commencement and sustenance of spermatogenesis (Cai et al., 2014; Griffeth et al., 2014; Kaur et al., 2018; Kim and Moley, 2008; MacLean et al., 2013; Sakkas et al., 1993).

According to a past study, after inspecting GLUT expression of GLUT 8 and GLUT9 from the sperm and testis sample collected from genetically modified diabetic mice, it has been demonstrated that the mice is lacking in GLUT9 protein and has decreased sperm motility with lower fertilization rates. The above-mentioned study demonstrated that both glucose and insulin are essential in the process of maturation of sperm and movement of sugar in the sperm which also controls motility of sperm during capacitation and fertilization. This finding is suggested by the author that a deficit of insulin or hyperglycemia impaired Glut9 transcription. When the same mice were treated with insulin motility and concentration of sperm increased proving that insulin signaling plays a chief role in improving sperm quality. Glucose is required for fertilization and is necessary for sperm oocyte binding and subsequently embryo viability in the mouse (Salminen et al., 2015; Ulisse et al., 1992; Zhang et al., 2013a).

### 3.1. Insulin resistance effect on DM males

In T2DM persons, insulin resistance (IR) is a principal pathogenic element (Kaur et al., 2018). IR and reproductive hormones are intriguingly connected, INS sensitivity is affected by reproductive hormones while androgens can enhance IR, slowing down DM development. In a person affected with DM, T levels are much less than in normal people (Agbaje et al., 2007). IR is the main linking factor between T and DM. As androgen level decreases, IR increase leading to DM. Inflammatory factors like serum triglycerides, TNF- $\alpha$ , interleukin-6, and others (Cai et al., 2014) are decreased due to Dehydroepiandrosterone (DHEA). According to a study, in a group of non-diabetic aged men, it was observed that the occurrence of DM is lower in a person who has a high level of total testosterone and free testosterone, and sex hormone binding protein (SHBG) (Salminen et al., 2015). In DM patients, the quantity of free testosterone, total testosterone and SHBG decreases compared to healthy people (Cree-Green et al., 2015; Zhang et al., 2013a). T facilitates the uptake of glucose, glycolysis, and oxidative phosphorylation. Testosterone also enhances insulin resistance by increasing the movement of glucose, restricting inflammatory feedback, aiding mitochondrial role, and restricting adipocyte and tissue amplification. INS sensitivity is maintained by T.

### 4. Effect of DM on the endocrine system (Role of hypothalamus pituitary-testicular axis)

In the conventional operating hypothalamus pituitary testicular axis, GnRH is released by the hypothalamus which further activates the anterior pituitary to release LH and FSH. FSH and LH target the Sertoli cells and the Leydig cells, subsequently, activating the spermatogenesis activity. HPG axis is disrupted with the outbreak of diabetes, leading to impaired spermatogenesis, and ensuing subfertility (Cree-Green et al., 2015). Diabetic males have a low level of testosterone along with decreased levels of luteinizing hormone and follicle-stimulating

hormone. LHRH producing hypothalamic cells doesn't function rightly to the feedback when the amount of testosterone decreases. This impotence in flawless response of the pituitary to serum testosterone level declines signifies that elevation in serum glucose has a principal consequence on the association of the endocrine system and nervous system. Serum luteinizing hormone and follicle-stimulating hormone decline may be due to defects in its synthesis and release (Schoeller et al., 2012). Serum testosterone level is decreased due to an increase in body lipids caused by diabetes which occurs because of the activities of the aromatase enzyme in the fat tissues afterward convert testosterone and androstenedione to estrogens (Emanuele and Emanuele, 2001). So, in diabetic males, besides a decrease in serum testosterone synthesis and metabolism, excessive testosterone and androstenedione are transformed into estradiol and estrone, respectively which may lead to a decrease in testosterone level. As the level of estrogens increases, it strives a negative feedback effect on LH and FSH production and may subsidize the repression of these crucial reproductive hormones. CNS does get affected by serum insulin and this also affects the homeostasis of the whole body as well as the reproductive axis via signaling the pituitary and the testis. Regulation of the HPG axis is dramatically affected by insulin levels. The influence of diabetes is mediated by signaling in the brain on the reproductive axis. Insulin binds with insulin receptors which results in a signaling cascade. As a result of interactions between insulin receptors substrate proteins IRS-2, insulin potentiates signaling through phosphatidylinositol 3-kinase (PI3-kinase), which later initiates PKB (Protein kinase B), which is a chief component of energy signaling (Pritchard et al., 1998). Multiple sites in the brain show insulin signaling. In the hypothalamus, the olfactory bulb and the pituitary, insulin receptor expression is present (Boura-Halfon and Zick, 2009). In addition to this, the concentration of insulin is higher in the brain than insulin in the plasma, which proves that insulin plays a key role in the functioning of the CNS (Boura-Halfon and Zick, 2009). The exact repercussions of insulin level on the reproductive axis are yet to be demonstrated. Hyperinsulinaemia (influenced by hyperinsulinaemic clamp) trigger luteinizing hormones released in the animals, which shows the hypothalamic action of gonadotropin-releasing hormones (Salvi et al., 2006). In the same study it has been reported that in the culture of hypothalamic neurons, GnRH release and expression were stimulated directly and dose-dependently by insulin (Bruning et al., 2000) (Obici et al., 2002). The histological study also disclosed that many of the seminiferous tubules seem normal and approximately 20 % don't own a lumen having hardly any mature spermatozoa. Leydig cell population shrunk due to the deficiency of insulin signaling in the brain which lowers the hormonal output required to maintain the population of Leydig cells to promote spermatogenesis in all tubules (Zhang et al., 2013b). In the brain, insulin signaling is required for suppressing glucose fabrication. For the increased glucose production injection of insulin signaling inhibitors is used. This experiment shows that insulin acts on the neuron is synchronized independently from plasma insulin and it may be required in whole energy homeostasis regulated by the CNS (Barash et al., 1996).

The role of insulin on the reproductive axis is not the only type of interaction that is controlled by insulin receptors in the brain. The level of serum insulin is related to circulating amount of leptin directly which is a chief molecule helping in regulating energy homeostasis. Fat cells secrete leptin which plays an important role in signaling in the hypothalamus thereby regulating the reproductive system. It sends metabolic signals to the brain informing nutritional status and animals' ability to regulate the energy demand of reproduction (Barr et al., 1997). *In vitro*, insulin directly affects leptin synthesis (Cammisotto and Bukowiecki, 2002; Kolaczynski et al., 1996; Wabitsch et al., 1996). Leptin production is increased after insulin administration in fat cells, *in vitro*. Circulating leptin levels are increased after prolonged exposure to hyperinsulinemia, *in vivo* (Azar et al., 2002). In T1DM patients, leptin levels get affected. In newly diagnosed T1DM patients leptin levels get decreased before the start of insulin treatment, which gets normalized

after the administration of insulin treatment (Hanaki et al., 1999). In summary, serum leptin is managed by insulin amount (Roy et al., 2015) and therefore influences the reproductive axis.

Various studies have shown the connection between DM and HPG axis disruption which affects the concentration of testosterone, FSH and LH in males (Fig. 2). In T1DM men, the HPG axis is suppressed as a result FSH and LH levels also decrease (Baccetti et al., 2002). In the case of T2DM, shrunken Leydig cells reduces testosterone secretion (Suresh and Prakash, 2012).

## 5. Effect of neuropathy and infectious on DM males

About 50 % of diabetic men have been affected with diabetic neuropathies especially peripheral neuropathies (De Angelis et al., 2001; Tesfaye and Selvarajah, 2012). It causes secondary infertility and erectile dysfunction. Penile erection naturally needs an entire cavernous nerve. Besides this, penile erection initiation and maintenance require neuronal nitric oxide synthase (nNOS).

In DM males, various infections also affect the reproductive system which can cause infertility in them. Gangrene and balanitis affect penis in DM. Calcification of the vas deferens may also lead to complications. Abscess and intertrigo of scrotum care were also reported in DM males (Gandhi et al., 2017).

## 6. Effect of DM on spermatogenesis and sperm

Semen analyses in DM males have shown declined density, motility, and abnormal morphology. Neuropathy, oxidative stress and endocrine disruption cause this deterioration in sperm parameters (Ramalho-Santos et al., 2008). This can cause a rise in infertility and subfertility in men affected with diabetes (Delfino et al., 2007; La Vignera et al., 2011; Ramalho-Santos et al., 2008). BTB (Sertoli cell barrier) can also severely affect spermatogenesis. It divides the seminiferous epithelium into 2 compartments i.e., basal and apical epithelium, in which different stages of germ cells develop (Alves et al., 2013). BTB is

mainly dependent on hormone control and glucose metabolism. So, in the case of diabetes, glucose metabolism is disrupted which leads to impairment in BTB activity, causing depression of testicular structure, spermatogenesis and fertility (Alves et al., 2013). Spermatozoa in diabetes mellitus have defective mitochondria due to oxidative stress which suppresses motility and fertility (Kao et al., 1998; Ramalho-Santos et al., 2008). Oxidative stress also damages DNA causing apoptosis of germ cells and declining sperm counts (Kao et al., 1998). In a study, it was reported that diabetic males semen has a high amount of nuclear and mitochondrial damage as compared to healthy individuals (Agbaje et al., 2007). In another study, DM men had a high amount of ROS and DNA damage chemicals, nitrate/nitrite and 8-OHdG (8-hydroxydeoxyguanosine) (Amiri et al., 2011). The level of Malondialdehyde (a marker of oxidative stress) also rises in infertile diabetic men (La Vignera et al., 2012). It is important to note that the mechanism involves in the change of sperm parameters in T1DM and T2DM are different. T1DM sperm are altered by autoimmune whereas T2DM sperm alteration is caused by many factors involving metabolic syndrome and alteration in testosterone.

## 7. Possible damaging pathways

### 7.1. Role of mitochondria and ROS

Oxidative stress is majorly involved in several complications in DM (Kanter et al., 2012, 2013). It is commonly linked with infertility in males. Recent studies reported that 25–40 % of infertile males' semen samples contain high amount of ROS which causes degradation of sperm quality and function. Spermatozoa plasma membrane consists of a high amount of PUFA (polyunsaturated fatty acids) and a little amount of scavenging enzymes are present in their cytoplasm so it is more sensitive to free radicals oxidation in contrast to somatic cells (Chapman, 2008; Sato et al., 2016). According to research, it has been concluded that a hyperglycemic state can cause a rise in the oxidation of mitochondrial glucose by producing a massive volume of superoxide and some free

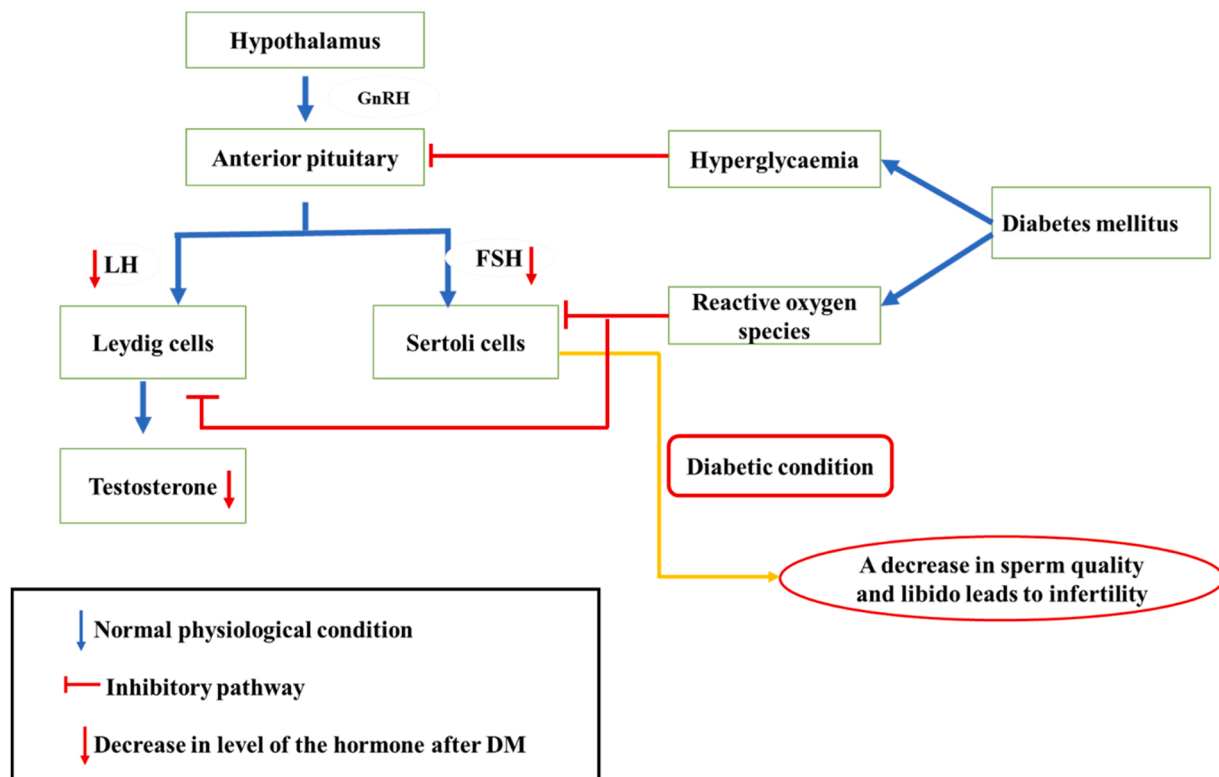


Fig. 2. Hypothalamic-pituitary testis axis regulation in Diabetes Mellitus male's reproduction.

radicals into the cytosol (Roy et al., 2015). ROS in testis is generated by mitochondrial NADPH oxidase which leads to the production of superoxide (Kwak et al., 2003). The activated NADPH oxidase family affects diabetic testopathy negatively (Sabeur and Ball, 2007; Zhang et al., 2012). Vitamin C and calciferol (non-enzymatic antioxidants) inhibit the action of reactive oxygen species on sperm generating abnormal spermatozoa (Ding et al., 2016). Activated receptors of endothelin A and B (ET A and ET B) modify the function of testicles (Qiuling, 2007). After activation of NADPH oxidase, ET-1 enhances the production of ROS in germ cells (Brewer et al., 2011; Li et al., 2015). The transcription of prepro-endothelin1 (ppET1), ET converting enzyme (ECE), and ET receptors is promoted by oxidative stress which is caused by increased ROS production (Kanter et al., 2012). The ET system with ROS generating system works in sync causing oxidative stress in a cyclic manner (Chapman, 2008). Irregularities in ROS production and catabolism halt the process of spermatogenesis and the apoptosis of germ cells causing a decline in sperm count (Roy et al., 2015; Wang et al., 2014). Studies showed that flawed spermatogenesis is caused by faulty signaling of Nrf 2 (nuclear factor-erythroid 2-related factor 2) (Kovac et al., 2015). In DM, Nrf 2 gene is downregulated in the testis which plays an important part in oxidative defense (Wang et al., 2014). ARE (antioxidant response element)-dependent pathway can control the oxidant overproduction and detrimental ROS production by catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) (Kannan et al., 2015; Kumar et al., 2002).

Intriguingly, in human and animal tissue, mtDNA (mitochondrial DNA) is more prone to impairment than nDNA (nuclear DNA). ROS can cause extensive deletions in mtDNA strands. Defective mitochondrial spermatozoa produce inefficient ATP leading to oxidative stress inducing crisis of energy leading to a decrease in motility and fertility (Sajad et al.). Defects in mitochondrial respiration lead to arrest in meiosis and irregularities in sperm morphology, making it necessary for the presence of mitochondrial respiratory function in the process of spermatogenesis in mammals (Nakada et al., 2006).

### 7.2. Germ cell apoptosis

In both T1DM and T2DM, apoptosis of germ cells happens in the male gonads. Recent research concludes that in infertile diabetic males, there is a definite relation between increased ROS damaged sperm and cytochrome c, caspase 9 and 3 high level (Bayram et al., 2016). In DM,

apoptosis of germ cell is arbitrated by 2 pathways leading to reproductive disorder: the extrinsic death receptor pathway and the intrinsic mitochondrial pathway. Molecules from any one of the pathways can affect the alternative pathways. The main focus of the apoptosis study is the endogenous apoptosis pathway (Fig. 3). Cytochrome c is released by the mitochondrial intrinsic pathway. Cytochrome c is released into the cytosol by increased levels of reactive oxygen species which destruct both the membranes of mitochondria and lead to the production of apoptosome (complex of ATP, Apaf-1 and procaspase-9) (Zhao et al., 2015). Apoptosome promotes the stimulation of procaspase-9 automatically, afterwards procaspase-3 is activated (Zhao et al., 2015). Germ cell enters into apoptosis after the activation of caspase 3. Apoptosis is initiated by the extrinsic signaling pathway through interactions transport membrane receptors, in this process members of the TNF (tumor necrosis factor) receptor gene superfamily are engaged. In the testis, low levels of TNF- $\alpha$  is present in physiological conditions (Torchinsky et al., 2004). During various stages of reproductive dysfunction production of testicular TNF- $\alpha$  is observed (Ibrahim et al., 2013). ROS independent pathways can also start apoptosis in sperm involving Fas (cell surface protein). Samples containing a lower concentration of sperm had increased chances of containing Fas-positive spermatozoa (Pentikäinen et al., 2001). Till date, TNFa/TNFR1, FasL/FasR, Apo2L/DR4, Apo3L/DR3 and Apo2L/DR5 are best characterized death receptors and their corresponding ligands. Many diabetic complications are caused by these receptors as insulin resistance is caused by TNF- $\alpha$ . In conclusion, the above-mentioned mitochondrial apoptosis processes are regulated via components of the proteins Bcl-2 family. p53 plays an essential part in the Bcl-2 family protein regulation. The exact mechanism of this process is yet to be completely known.

### 7.3. Germ cell autophagy

Autophagy is necessary for metabolic processes and when it becomes abnormal it leads to diseases related to metabolisms such as diabetes and its complications (Quan et al., 2013). It is intrinsic to the activities of testicles and its insufficiency can cause degeneration of germ cells and disturb the homeostasis inside the cells by degrading and modifying mitochondria and endoplasmic reticulum (ER) (Sato et al., 2016). Primarily it was believed that autophagy is a pro-survival mechanism that cells initiate while having a stress state. But after collecting several evidences it is now known that autophagy can also contribute to apoptosis

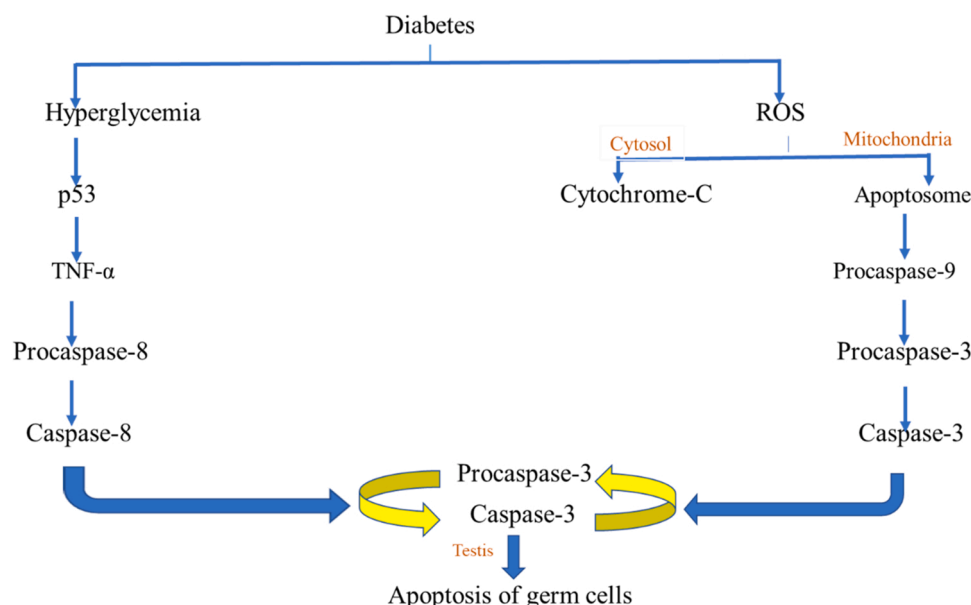


Fig. 3. Mechanism of germ cell apoptosis in diabetic males.

(Rubinsztein et al., 2012). Hyperglycemia induces mitochondrial glucose oxidation releases a large quantity of superoxide and some other free radicals inside the cytoplasm. In mitochondria, surplus ROS causes the apoptosis of germ cells and can hinder the process of spermatogenesis (Kumar et al., 2002). Some of the critical upstream events in autophagy are chronic intracellular stress (mitochondria or ER stress). Experiments conducted on animals have shown that the ER stress or oxidative stress in the early stages can cause adaptive autophagy upregulation which helps in restoring homeostasis inside the cells by destroying many harmful molecules like unfolded or misfolded protein molecules in the lumen of ER, cytosolic proteins damage by ROS, some malfunction mitochondria, and ERs. Prolonged autophagy upregulation can progress into defective autophagy when intracellular stresses remain unresolved for a long time (Muriach et al., 2014). Both the mitochondrial and ER level autophagy is affected by diabetes but the role of autophagy in reproductive injury and metabolism caused by diabetes isn't understood clearly. Therefore, it is currently being further investigated that, what parts are played by autophagy in the pathogenesis of diabetes complications.

## 8. Biomarkers of diabetes-associated infertility in males

### 8.1. Reproductive hormones

In diabetes-associated infertility, the level of reproductive hormones like follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone decreases. DM suppresses the activity of the HPG axis which ultimately causes a decline in FSH and LH levels (Erol et al., 2002). The function of Leydig cells also declined in the case of DM which causes a decrease in the level of testosterone (Pitteloud et al., 2005).

### 8.2. Steroidogenic acute regulatory protein (StAR)

StAR chiefly mediates the biosynthesis of steroids. its expression remarkably decreases along with CYP11A1. Downregulation of StAR and CYP11A1 causes accumulation of cholesterol in the testis (Sm and Mahaboob Basha, 2017).

### 8.3. Hydroxysteroid dehydrogenase

The level of hydroxysteroid dehydrogenase (HSD) decreases in diabetes-associated reproductive dysfunction. The expression of  $3\beta$ -HSD and  $17\beta$ -HSD is downregulated, and this causes a rise in testicular cholesterol.

### 8.4. AGE (advanced glycation end products)

AGE level rises in hyperglycemia which may cause penis vascular dysfunction. This deteriorates the function of erection (Awad et al., 2010; Kamdar and Shah, 2014).

### 8.5. Protein expression of lactate dehydrogenase (LDH) and monocarboxylate transporter-4 (MCT4)

Lactate dehydrogenase activity decreases in the Sertoli cells. So, the genes associated with the metabolism and transport of lactate are downregulated. LDH and MCT4 protein expression decline besides LDH activity.

### 8.6. Antioxidant enzymes

The presence of antioxidants in testis confirms that steroidogenesis and spermatogenesis are not adversely affected by oxidative stress. In diabetic males, the level of antioxidant enzymes in the testis remarkably decreases whereas lipid peroxidation in the testis increases. In this case, the level of SOP, CAT and GPx decrease whereas MDA level rises.

### 8.7. Vascular endothelial growth factor (VEGF)

It is an angiogenic and neurotrophic growth factor that stimulates the growth of endothelial cells and raises the receptiveness of the vessel wall (Ebisch et al., 2008; Leung et al., 1989). It is produced in both Leydig and Sertoli cells. It is crucial in the homeostasis of germ cells. Its level decreases in diabetic males.

### 8.8. Neurotrophic factor (NGF)

It is a neurotrophic factor that controls a lot of crucial activity of the neurons. It encourages the motility of sperm and helps in acrosomal reactions of sperm cells. It also encourages testosterone production (Zhang, L. et al., 2013). It has a crucial part in the male reproductive system. In diabetic males, its level decreases.

## 9. Medicinal plants

Natural products are widely accepted for the treatment as compared to modern-day medicine due to their multiple arbitration targets for a particular disease (Sajad et al., 2020). Various natural products have been used to cope with DM and regulation of its associated biomarkers. Here, we have listed various plants those have detrimental roles in preventing and regulating DM-induced reproductive impairment in males (Table 3).

In the field of pharmacogenomics, understanding the regulation of a disease network is of critical interest for designing drugs against different diseases (Sajad et al., 2022a). Various phytochemicals are isolated from these plants, and they have also been used to check their role against different diseases including infertility (Sajad et al., 2022b). These phytochemicals have their roles in three levels in controlling the reproductive dysfunction of males. Some of them show pretesticular effect by increasing testosterone levels and this improves the production of normal and healthy sperms. At the testicular level, some plants show a decrease in the activity of LDH. Some plants have also shown a rise in StAR and  $17\beta$ -HSD expression. The increased expression of StAR protein causes more transportation of cholesterol to the mitochondria of Leydig cells for the synthesis of testosterone (Nah et al., 2012). It is also observed that some natural products improve sexual behavior and erectile dysfunction.

It is observed that many phytoconstituents have significantly reduce the blood sugar level of diabetic rats. It is also observed that medicinal plants also cause regeneration of pancreatic  $\beta$ -cells and improve insulin secretion and feasibility (Giribabu et al., 2014; Koneri et al., 2014). Thus, it has been suggested that these plant-based compounds show their substantial ability to prevent the onset of disease by regulating the expression of different biomarkers.

## 10. Conclusions

Till now the effect of DM on reproductive health is highly ignored. Many studies have shown that DM has a negative impact on male fertility, particularly the quality of sperm, semen constituents, sperm motility, and sperm DNA damage. It's possible that this may not only result in subfertility or infertility but will also pass to the offspring and cause in subfertility or infertility in them. Reproductive dysfunction is caused by several DM-related factors, including oxidative stress, disruption of the HPG axis, and apoptosis. All these elements lead to aberrant hormone production and affect the morphology of the testis and epididymis. They also result in a decrease in the amount and quality of Leydig, Sertoli, and germ cells, which further causes sperm to have aberrant morphology, count, and motility. This condition has also been linked to several biomarkers, including AGE, StAR, VEGF, etc. Numerous medicinal herbs have been shown to play a significant role in preventing and reducing the impact of DM on the male reproductive system. However, further research is needed to fully understand the



**Table 3**

List of plants use to manage reproductive impairment in diabetic males.

S. No.	Plant	Common name	Part used	Fasting blood glucose level	Effect on the reproduction system	Ref
1	<i>Amaranthus spinosus</i>	Prickly amaranth, kanta chaulai	Stem	Significant decrease	Weight of testicles, spermatogenesis, and testosterone increases	[42]
2	<i>Chlorophytum borivilianum</i>	safed musli	Root	Significant decrease	sperm normal morphology %, count, viability, and motility increase; sperm oxidative stress and apoptosis decreases	[151]
3	<i>Chlorophytum borivilianum</i>	safed musli	tuber	–	Sexual behavior increases	[152]
4	<i>Cinnamomum zeylanicum</i>	Cinnamon	bark	decrease	Increase in serum testosterone, motility, count, and visibility of sperm	[153]
5	<i>Curculigo orchioides</i>	Kali musli	–	Significant decrease	Rise in serum testosterone, penile erection index, sperm count, and sexual behavior improved	[154]
6	<i>Danae racemosa</i>	Alexandrian laurel	leaves	–	Rise in testicular weight and serum testosterone.	[155]
7	<i>Eugenia jambolana</i>	Jamun.	seeds	–	Rise in testicular weight, serum testosterone, and sperm count; in testis downregulation of Bax and upregulation of Bcl-2 expression; increase in regeneration of germ cell	[27]
8	<i>Mucuna pruriens</i>	Kauncha	seeds	Significant decrease	Rise in FSH, LH and testosterone level; rise in testicular, prostate, epididymis, and seminal vesicles weight; increase in DSP, sperm viability, motility, and count; sexual behavior and erectile function also increase.	[26]
9	<i>Musa paradisiaca</i>	banana	root	Significant decrease	Rise in testosterone; decrease in cholesterol of testis; increase in motility and count of sperm; rise in antioxidant of testicles, sperm and epididymis; apoptosis of germ cells in testis decreases and histology of testis ameliorated	[156]
10	<i>Withania somnifera</i>	Ashwagandha	root	Significant decrease	Increase in antioxidant enzymes and testicular weight, decrease in lipid peroxidation. testicular LDH and $\beta$ -HSD increases	[38]
11	<i>Zingiber officinale</i>	Ginger	root	decrease	Increase in sperm motility, count, viability and serum testosterone	[153]

effect of phytochemicals in preventing the pathophysiology of diabetes on male fertility. To clearly understand the impact of DM on the male reproductive system, future study must put detailed emphasis on molecular level.

### CRediT authorship contribution statement

Nida Andlib and Mohd Sajad designed and carried out the literature survey and writing work of this study and Dr. Sonu Chand Thakur and Dr. Rajesh Kumar supervised the writing work and edited the manuscript accordingly.

### Conflict of interest

Authors shows no conflict of interest.

### Acknowledgment

We would like to thank Jamia Millia Islamia for providing infrastructure, journal access, and internet facilities. Nida Andlib would like to thank Council of Scientific and Industrial Research for awarding Junior Research Fellowship.

### References

- Abdul-Ghani, M., Nawaf, G., Fawaz, G., Itzhak, B., Minuchin, O., Vardi, P., 2006. Increased prevalence of microvascular complications in type 2 diabetes patients with the metabolic syndrome. *IMAJ* 8 (6), 378.
- Agbaje, I., Rogers, D., McVicar, C., McClure, N., Atkinson, A., Mallidis, C., Lewis, S., 2007. Insulin dependant diabetes mellitus: implications for male reproductive function. *Hum. Reprod.* 22 (7), 1871–1877.
- Ahangarpour, A., Oroojan, A.A., Heidari, H., Ghaedi, E., Taherkhani, R., 2015. effects of hydro-alcoholic extract from *Arctium lappa* L.(burdock) root on gonadotropins, testosterone, and sperm count and viability in male mice with nicotinamide/streptozotocin-induced type 2 diabetes. *Malays. J. Med. Sci.* 22 (2), 25.
- Al-Roujaie, A., Abuhashish, H., Ahmed, M., Alkhamees, O., 2017. Effect of rutin on diabetic-induced erectile dysfunction: possible involvement of testicular biomarkers in male rats. *Andrologia* 49 (8), e12737.
- Alves, M.G., Martins, A.D., Cavaco, J.E., Socorro, S., Oliveira, P.F., 2013. Diabetes, insulin-mediated glucose metabolism and Sertoli/blood-testis barrier function. *Tissue Barriers* 1 (2), e23992.
- Amiri, I., Karimi, J., Piri, H., Goodarzi, M.T., Tavilani, H., Khodadadi, I., Ghorbani, M., 2011. Association between nitric oxide and 8-hydroxydeoxyguanosine levels in semen of diabetic men. *Syst. Biol. Reprod. Med.* 57 (6), 292–295.
- Awad, H., Salem, A., Gadalla, A., Abou El Wafa, N., Mohamed, O., 2010. Erectile function in men with diabetes type 2: correlation with glycemic control. *Int. J. Impot. Res.* 22 (1), 36–39.
- Azar, S., Zalloua, P., Zantout, M., Shahine, C., Salti, I., 2002. Leptin levels in patients with type 1 diabetes receiving intensive insulin therapy compared with those in patients receiving conventional insulin therapy. *J. Endocrinol. Investig.* 25 (8), 724–726.
- Baccetti, B., La Marca, A., Piomboni, P., Capitani, S., Bruni, E., Petraglia, F., De Leo, V., 2002. Insulin-dependent diabetes in men is associated with hypothalamo-pituitary derangement and with impairment in semen quality. *Hum. Reprod.* 17 (10), 2673–2677.
- Ballester, J., Muñoz, M.C., Domínguez, J., Rigau, T., Guinovart, J.J., Rodríguez-Gil, J.E., 2004. Insulin-dependent diabetes affects testicular function by FSH-and LH-linked mechanisms. *J. Androl.* 25 (5), 706–719.
- Barash, I.A., Cheung, C.C., Weigle, D.S., Ren, H., Kabigting, E.B., Kuijper, J.L., Clifton, D. K., Steiner, R.A., 1996. Leptin is a metabolic signal to the reproductive system. *Endocrinology* 137 (7), 3144–3147.
- Barr, V.A., Malide, D., Zarnowski, M.J., Taylor, S.I., Cushman, S.W., 1997. Insulin stimulates both leptin secretion and production by rat white adipose tissue. *Endocrinology* 138 (10), 4463–4472.
- Bayram, S., Kizilay, G., Topcu-Tarlacalisir, Y., 2016. Evaluation of the Fas/FasL signaling pathway in diabetic rat testis. *Biotech. Histochem.* 91 (3), 204–211.
- Borland, K., Mita, M., Oppenheimer, C., Blinderman, L., Massague, J., Hall, P., Czech, M., 1984. The actions of insulin-like growth factors I and II on cultured Sertoli cells. *Endocrinology* 114 (1), 240–246.
- Boura-Halfon, S., Zick, Y., 2009. Phosphorylation of IRS proteins, insulin action, and insulin resistance. *Am. J. Physiol. -Endocrinol. Metab.* 296 (4), E581–E591.
- Boussouar, F., Benahmed, M., 2004. Lactate and energy metabolism in male germ cells. *Trends Endocrinol. Metab.* 15 (7), 345–350.
- Brewer, J., Wallace, K., Roberts, L., Ray, L., Martin, J., LaMarca, B., Wallukat, G., Dechend, R., 2011. 763: AT1-AA increases AngII-induced ET-1 and ROS. *Am. J. Obstet. Gynecol.* 204 (1), S300.
- Bruning, J.C., Gautam, D., Burks, D.J., Gillette, J., Schubert, M., Orban, P.C., Klein, R., Krone, W., Muller-Wieland, D., Kahn, C.R., 2000. Role of brain insulin receptor in control of body weight and reproduction. *Science* 289 (5487), 2122–2125.
- Bucci, D., Rodríguez-Gil, J.E., Vallorani, C., Spinaci, M., Galeati, G., Tamanini, C., 2011. GLUTs and mammalian sperm metabolism. *J. Androl.* 32 (4), 348–355.
- Burant, C., Davidson, N., 1994. GLUT3 glucose transporter isoform in rat testis: localization, effect of diabetes mellitus, and comparison to human testis. *Am. J. Physiol. -Regul., Integr. Comp. Physiol.* 267 (6), R1488–R1495.
- Cai, X., Tian, Y., Wu, T., Cao, C.-X., Li, H., Wang, K.-J., 2014. Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Asian J. Androl.* 16 (1), 146.
- Cameron, D., Rountree, J., Schultz, R., Repetta, D., Murray, F., 1990. Sustained hyperglycemia results in testicular dysfunction and reduced fertility potential in BBWCR diabetic rats. *Am. J. Physiol. -Endocrinol. Metab.* 259 (6), E881–E889.
- Cammisotto, P.G., Bukowiecki, L.J., 2002. Mechanisms of leptin secretion from white adipocytes. *Am. J. Physiol. -Cell Physiol.* 283 (1), C244–C250.
- Carosa, E., Radico, C., Giansante, N., Rossi, S., D'ADAMO, F., Di Stasi, S.M., Lenzi, A., Jannini, E.A., 2005. Ontogenetic profile and thyroid hormone regulation of type-1 and type-8 glucose transporters in rat Sertoli cells. *Int. J. Androl.* 28 (2), 99–106.

- Chapman, S., 2008. Mechanisms of endothelin-1 induced reactive oxygen species production in vascular adventitial fibroblasts.
- Cree-Green, M., Newcomer, B.R., Coe, G., Newnes, L., Baumgartner, A., Brown, M.S., Pyle, L., Reusch, J.E., Nadeau, K.J., 2015. Peripheral insulin resistance in obese girls with hyperandrogenism is related to oxidative phosphorylation and elevated serum free fatty acids. *Am. J. Physiol. -Endocrinol. Metab.* 308 (9), E726–E733.
- De Angelis, L., Marfella, M., Siniscalchi, M., Marino, L., Nappo, F., Giugliano, F., De Lucia, D., Giugliano, D., 2001. Erectile and endothelial dysfunction in type II diabetes: a possible link. *Diabetologia* 44 (9), 1155–1160.
- De Young, L., Yu, D., Bateman, R.M., Brock, G.B., 2004. Oxidative stress and antioxidant therapy: their impact in diabetes-associated erectile dysfunction. *J. Androl.* 25 (5), 830–836.
- Delfino, M., Imbrogno, N., Elia, J., Capogreco, F., Mazzilli, F., 2007. Prevalence of diabetes mellitus in male partners of infertile couples. *Minerva Urol. e Nefrol. = Ital. J. Urol. Nephrol.* 59 (2), 131–135.
- Ding, C., Wang, Q., Hao, Y., Ma, X., Wu, L., Li, W., Wu, Y., Guo, F., Ma, S., Huang, F., 2016. Vitamin D supplement improved testicular function in diabetic rats. *Biochem. Biophys. Res. Commun.* 473 (1), 161–167.
- Dinulovic, Z., Radonjic, G., 1990. Diabetes mellitus/male infertility. *Arch. Androl.* 25 (3), 277–293.
- Ebisch, I.M., Thomas, C.M., Wetzels, A.M., Willemsen, W.N., Sweep, F.C., Steegers-Theunissen, R.P., 2008. Review of the role of the plasminogen activator system and vascular endothelial growth factor in subfertility. *Fertil. Steril.* 90 (6), 2340–2350.
- Emanuele, M.A., Emanuele, N., 2001. Alcohol and the male reproductive system. *Alcohol Res. Health* 25 (4), 282.
- Erol, B., Tefekli, A., Ozbey, I., Salman, F., Dincag, N., Kadioglu, A., Tellaloglu, S., 2002. Sexual dysfunction in type II diabetic females: a comparative study. *J. Sex. Marital Ther.* 28 (sup1), 55–62.
- Fedder, J., Kaspersen, M.D., Brandslund, I., Højgaard, A., 2013. Retrograde ejaculation and sexual dysfunction in men with diabetes mellitus: a prospective, controlled study. *Andrology* 1 (4), 602–606.
- Fode, M., Krogh-Jespersen, S., Brackett, N.L., Ohl, D.A., Lynne, C.M., Sønksen, J., 2012. Male sexual dysfunction and infertility associated with neurological disorders. *Asian J. Androl.* 14 (1), 61.
- Frenkel, G., Peterson, R., Freund, M., 1973. Changes in the metabolism of guinea pig sperm from different segments of the epididymis. *Proc. Soc. Exp. Biol. Med.* 143 (4), 1231–1236.
- Galarido, M.N., Riera, M.F., Pellizzari, E.H., Chemes, H.E., Venara, M.C., Cigorraga, S.B., Meroni, S.B., 2008. Regulation of expression of Sertoli cell glucose transporters 1 and 3 by FSH, IL1 $\beta$ , and bFGF at two different time-points in pubertal development. *Cell Tissue Res.* 334 (2), 295–304.
- Gandhi, J., Dagur, G., Warren, K., Smith, N.L., Khan, S.A., 2017. Genitourinary complications of diabetes mellitus: an overview of pathogenesis, evaluation, and management. *Curr. Diabetes Rev.* 13 (5), 498–518.
- Gaunay, G., Nagler, H.M., Stember, D.S., 2013. Reproductive sequelae of diabetes in male patients. *Endocrinology and Metabolism. Endocrinol. Metab. Clin.* 42 (4), 899–914.
- Ghlissi, Z., Hamden, K., Saoudi, M., Sahnoun, Z., Zeghal, K.M., El Feki, A., Hakim, A., 2012. Effect of *Nigella sativa* seeds on reproductive system of male diabetic rats. *Afr. J. Pharm. Pharmacol.* 6 (20), 1444–1450.
- Ghosh, A., Jana, K., Ali, K., De, D., Chatterjee, K., Ghosh, D., 2014. Corrective role of *Eugenia jambolana* on testicular impairment in streptozotocin-induced diabetic male albino rat: An approach through genomic and proteomic study. *Andrologia* 46 (3), 296–307.
- Giribabu, N., Kumar, K.E., Rekha, S.S., Muniandy, S., Salleh, N., 2014. Chlorophytum borivilianum root extract maintains near normal blood glucose, insulin and lipid profile levels and prevents oxidative stress in the pancreas of streptozotocin-induced adult male diabetic rats. *Int. J. Med. Sci.* 11 (11), 1172.
- Gobbo, M.G., Costa, C.F.P., Silva, D.G.H., de Almeida, E.A., Góes, R.M., 2015. Effect of melatonin intake on oxidative stress biomarkers in male reproductive organs of rats under experimental diabetes. *Oxid. Med. Cell. Longev.* 2015.
- Gonzales, G.F., Gonzales-Castaneda, C., Gasco, M., 2013. A mixture of extracts from Peruvian plants (black maca and yacon) improves sperm count and reduced glycemia in mice with streptozotocin-induced diabetes. *Toxicol. Mech. Methods* 23 (7), 509–518.
- Griffith, R.J., Bianda, V., Nef, S., 2014. The emerging role of insulin-like growth factors in testis development and function. *Basic Clin. Androl.* 24 (1), 1–10.
- Hafez, D.A., 2010. Effect of extracts of ginger roots and cinnamon bark on fertility of male diabetic rats. *J. Am. Sci.* 6 (10), 940–947.
- Hanaki, K., Becker, D.J., Arslanian, S.A., 1999. Leptin before and after insulin therapy in children with new-onset type 1 diabetes. *J. Clin. Endocrinol. Metab.* 84 (5), 1524–1526.
- Handberg, A., Vaag, A., Damsbo, P., Beck-Nielsen, H., Vinten, J., 1990. Expression of insulin regulatable glucose transporters in skeletal muscle from type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 33 (10), 625–627.
- He, Z., Yin, G., Li, Q.Q., Zeng, Q., Duan, J., 2021. Diabetes mellitus causes male reproductive dysfunction: a review of the evidence and mechanisms. *In vivo* 35 (5), 2503–2511.
- Hecht, M.J., Neundörfer, B., Kiesewetter, F., Hilz, M.J., 2001. Neuropathy is a major contributing factor to diabetic erectile dysfunction. *Neurol. Res.* 23 (6), 651–654.
- Ibrahim, M.N., Asalah, A.K., Abd-Alaleem, D.I., Moursi, S.M., 2013. Effect of ghrelin on testicular functions in streptozotocin induced type 1 diabetic rats. *Int. J. Diabetes Res.* 2 (6), 101–111.
- Imani, M., Talebi, A., Fesahat, F., Rahiminia, T., Seifati, S., Dehghanpour, F., 2021. Sperm parameters, DNA integrity, and protamine expression in patients with type II diabetes mellitus. *J. Obstet. Gynaecol.* 41 (3), 439–446.
- Jiang, X., Zhang, C., Xin, Y., Huang, Z., Tan, Y., Huang, Y., Wang, Y., Feng, W., Li, X., Li, W., 2013. Protective effect of FGF21 on type 1 diabetes-induced testicular apoptotic cell death probably via both mitochondrial and endoplasmic reticulum stress-dependent pathways in the mouse model. *Toxicol. Lett.* 219 (1), 65–76.
- Jutte, N.H., Jansen, R., Grootegeed, J., Rommerts, F., Van der Molen, H., 1983. FSH stimulation of the production of pyruvate and lactate by rat Sertoli cells may be involved in hormonal regulation of spermatogenesis. *Reproduction* 68 (1), 219–226.
- Kamdar, V., Shah, J.H., 2014. Sexual dysfunction in diabetes. *Improv. Diabetes Care Clin.* 312.
- Kamischke, A., Nieschlag, E., 2002. Update on medical treatment of ejaculatory disorders. *Int. J. Androl.* 25 (6), 333–344.
- Kannan, A., Ramachandirin, B., Sadasivam, M., Balakrishnan, S., 2015. Pralathan in role of oxidative stress on testicular aquaporins expression in hyperglycemic rats. *World Congr. Diabetes India* 1–5.
- Kanter, M., Aktas, C., Erbog, M., 2012. Protective effects of quercetin against apoptosis and oxidative stress in streptozotocin-induced diabetic rat testis. *Food Chem. Toxicol.* 50 (3–4), 719–725.
- Kanter, M., Aktas, C., Erbog, M., 2013. Curcumin attenuates testicular damage, apoptotic germ cell death, and oxidative stress in streptozotocin-induced diabetic rats. *Mol. Nutr. Food Res.* 57 (9), 1578–1585.
- Kao, S.-H., Chao, H.-T., Wei, Y.-H., 1998. Multiple deletions of mitochondrial DNA are associated with the decline of motility and fertility of human spermatozoa. *Mol. Hum. Reprod.* 4 (7), 657–666.
- Kaur, G., Thompson, L.A., Babcock, R.L., Mueller, K., Dufour, J.M., 2018. Sertoli cells engineered to express insulin to lower blood glucose in diabetic mice. *DNA Cell Biol.* 37 (8), 680–690.
- Kim, S.T., Moley, K.H., 2008. Paternal effect on embryo quality in diabetic mice is related to poor sperm quality and associated with decreased glucose transporter expression. *Reproduction* 136 (3), 313–322.
- Klip, A., Tsakiridis, T., Marette, A., Ortiz, P.A., 1994. Regulation of expression of glucose transporters by glucose: a review of studies in vivo and in cell cultures. *FASEB J.* 8 (1), 43–53.
- Kokk, K., Veräjänkorka, E., Wu, X.-K., Tapfer, H., Pöldoja, E., Pöllänen, P., 2004. Immunohistochemical detection of glucose transporters class I subfamily in the mouse, rat and human testis. *Medicina* 40 (2), 156–160.
- Kolaczynski, J.W., Nyce, M.R., Considine, R.V., Boden, G., Nolan, J.J., Henry, R., Mudaliar, S.R., Olefsky, J., Caro, J.F., 1996. Acute and chronic effect of insulin on leptin production in humans: studies in vivo and in vitro. *Diabetes* 45 (5), 699–701.
- Koneri, R.B., Samaddar, S., Ramaiah, C.T., 2014. Antidiabetic activity of a triterpenoid saponin isolated from *Momordica cymbalaria* Fenzl.
- Kovac, S., Angelova, P.R., Holmström, K.M., Zhang, Y., Dinkova-Kostova, A.T., Abramov, A.Y., 2015. Nrf2 regulates ROS production by mitochondria and NADPH oxidase. *Biochim. Biophys. Acta (BBA)-Gen. Subj.* 1850 (4), 794–801.
- Kumar, T.R., Doreswamy, K., Shrilatha, B., 2002. Oxidative stress associated DNA damage in testis of mice: induction of abnormal sperms and effects on fertility. *Mutat. Res./Genet. Toxicol. Environ. Mutagen.* 513 (1–2), 103–111.
- Kwak, J.M., Mori, I.C., Pei, Z.-M., Leonhardt, N., Torres, M.A., Dangl, J.L., Bloom, R.E., Bodde, S., Jones, J.D., Schroeder, J.I., 2003. NADPH oxidase AtrbohD and AtrbohF genes function in ROS-dependent ABA signaling in Arabidopsis. *EMBO J.* 22 (11), 2623–2633.
- Kyathanahalli, C.N., Manjunath, M.J., 2014. Oral supplementation of standardized extract of *Withania somnifera* protects against diabetes-induced testicular oxidative impairments in prepubertal rats. *Protoplasma* 251 (5), 1021–1029.
- La Vignera, S., Condorelli, R., Vicari, E., D'Agata, R., Calogero, A., 2011. Diabetes and sperm parameters: a brief review. *J. Androl.* 33, 145–153.
- La Vignera, S., Condorelli, R., Vicari, E., D'Agata, R., Salemi, M., Calogero, A., 2012. High levels of lipid peroxidation in semen of diabetic patients. *Andrologia* 44, 565–570.
- Leung, D.W., Cachianes, G., Kuang, W.-J., Goeddel, D.V., Ferrara, N., 1989. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science* 246 (4935), 1306–1309.
- Li, H., Yu, Y., He, W., Zhou, Y., Chai, J., 2015. Effects of activation of ALDH2 by ethanol in testis injury of type 2 diabetic rats. *Chin. Pharmacol. Bull.* 962–966.
- Long, L., Wang, J., Lu, X., Xu, Y., Zheng, S., Luo, C., Li, Y., 2015. Protective effects of scutellarin on type II diabetes mellitus-induced testicular damages related to reactive oxygen species/Bcl-2/Bax and reactive oxygen species/microcirculation/staving pathway in diabetic rat. *J. Diabetes Res.* 2015.
- MacLean, J.A., Hu, Z., Welborn, J.P., Song, H.-W., Rao, M.K., Wayne, C.M., Wilkinson, M.F., 2013. The RHOX homeodomain proteins regulate the expression of insulin and other metabolic regulators in the testis. *J. Biol. Chem.* 288 (48), 34809–34825.
- Malavige, L.S., Jayaratne, S.D., Kathiriarachchi, S.T., Sivayogan, S., Fernando, D.J., Levy, J.C., 2008. Erectile dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. *J. Sex. Med.* 5 (9), 2125–2134.
- Mancine, R., Penhos, J., Izquierdo, I., Heinrich, J., 1960. Effects of acute hypoglycemia on rat testis. *Proc. Soc. Exp. Biol. Med.* 104 (4), 699–702.
- Maresch, C.C., Stute, D.C., Alves, M.G., Oliveira, P.F., de Kretser, D.M., Linn, T., 2018. Diabetes-induced hyperglycemia impairs male reproductive function: a systematic review. *Hum. Reprod. Update* 24 (1), 86–105.
- Meller, S.M., Stip, E., Walker, C.N., Mena-Hurtado, C., 2013. The link between vasculogenic erectile dysfunction, coronary artery disease, and peripheral artery disease: role of metabolic factors and endovascular therapy. *J. Invasive Cardiol.* 25 (6), 313–319.
- Mohasseb, M., Ebied, S., Yehia, M.A., Hussein, N., 2011. Testicular oxidative damage and role of combined antioxidant supplementation in experimental diabetic rats. *J. Physiol. Biochem.* 67 (2), 185–194.

- Muriach, M., Flores-Bellver, M., Romero, F.J., Barcia, J.M., 2014. Diabetes and the brain: oxidative stress, inflammation, and autophagy. *Oxid. Med. Cell. Longev.* 2014.
- Nah, W.H., Koh, I.K., Ahn, H.S., Kim, M.J., Kang, H.-G., Jun, J.H., Gye, M.C., 2012. Effect of Spirulina maxima on spermatogenesis and steroidogenesis in streptozotocin-induced type I diabetic male rats. *Food Chem.* 134 (1), 173–179.
- Nakada, K., Sato, A., Yoshida, K., Morita, T., Tanaka, H., Inoue, S.-I., Yonekawa, H., Hayashi, J.-I., 2006. Mitochondria-related male infertility. *Proc. Natl. Acad. Sci. USA* 103 (41), 15148–15153.
- Nakayama, Y., Yamamoto, T., Abe, S.-I., 2004. IGF-I, IGF-II and insulin promote differentiation of spermatogonia to primary spermatocytes in organ culture of newt testes. *Int. J. Dev. Biol.* 43 (4), 343–347.
- Obici, S., Zhang, B.B., Karkanas, G., Rossetti, L., 2002. Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat. Med.* 8 (12), 1376–1382.
- Oliveira, P., Alves, M., Rato, L., Silva, J., Sa, R., Barros, A., Sousa, M., Carvalho, R., Cavaco, J., Socorro, S., 2011. Influence of 5 $\alpha$ -dihydrotestosterone and 17 $\beta$ -estradiol on human Sertoli cells metabolism. *Int. J. Androl.* 34 (6pt2), e612–e620.
- Oliveira, P., Alves, M., Rato, L., Laurentino, S., Silva, J., Sa, R., Barros, A., Sousa, M., Carvalho, R., Cavaco, J., 2012. Effect of insulin deprivation on metabolism and metabolism-associated gene transcript levels of in vitro cultured human Sertoli cells. *Biochim. Biophys. Acta (BBA)-Gen. Subj.* 1820 (2), 84–89.
- Pentikäinen, V., Erkkilä, K., Suomalainen, L., Ojala, M., Pentikäinen, M.O., Parvinen, M., Dunkel, L., 2001. TNF $\alpha$  down-regulates the Fas ligand and inhibits germ cell apoptosis in the human testis. *J. Clin. Endocrinol. Metab.* 86 (9), 4480–4488.
- Pitetti, J.-L., Calvel, P., Zimmermann, C., Conne, B., Papaioannou, M.D., Aubry, F., Cederroth, C.R., Urner, F., Fumel, B., Crausaz, M., 2013. An essential role for insulin and IGF1 receptors in regulating sertoli cell proliferation, testis size, and FSH action in mice. *Mol. Endocrinol.* 27 (5), 814–827.
- Pitteloud, N., Hardin, M., Dwyer, A.A., Valassi, E., Yialamas, M., Elahi, D., Hayes, F.J., 2005. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J. Clin. Endocrinol. Metab.* 90 (5), 2636–2641.
- Pritchard, J., Després, J.-P., Gagnon, J., Tchernof, A., Nadeau, A., Tremblay, A., Bouchard, C., 1998. Plasma adrenal, gonadal, and conjugated steroids before and after long term overfeeding in identical twins. *J. Clin. Endocrinol. Metab.* 83 (9), 3277–3284.
- Qiuling, X., 2007. Effects of extract ginkgo biloba on ROS of testis and epididymis and et of diabetic rats. *Journal of Mudanjang Medical College.*
- Quan, W., Jung, H.S., Lee, M.-S., 2013. Role of autophagy in the progression from obesity to diabetes and in the control of energy balance. *Arch. Pharmacol. Res.* 36 (2), 223–229.
- Ramallo-Santos, J., Amaral, S., Oliveira, P.J., 2008. Diabetes and the impairment of reproductive function: possible role of mitochondria and reactive oxygen species. *Curr. Diabetes Rev.* 4 (1), 46–54.
- Rato, L., Alves, M.G., Duarte, A.I., Santos, M.S., Moreira, P.L., Cavaco, J.E., Oliveira, P.F., 2015. Testosterone deficiency induced by progressive stages of diabetes mellitus impairs glucose metabolism and favors glycogenesis in mature rat Sertoli cells. *Int. J. Biochem. Cell Biol.* 66, 1–10.
- Reddy, K.P., Rao, Narayana, Murthy, M., Reddy, P.S., J., 2016. Lead aggravates the diabetic-induced reproductive toxicity in male Wistar rats. *Toxicol. Res.* 5 (5), 1465–1476.
- Riera, M.F., Galarido, M.N., Pellizzari, E.H., Meroni, S.B., Giorragia, S.B., 2009. Molecular mechanisms involved in Sertoli cell adaptation to glucose deprivation. *Am. J. Physiol. -Endocrinol. Metab.* 297 (4), E907–E914.
- Roy, V.K., Chenkual, L., Gurusubramanian, G., 2015. Protection of testis through antioxidant action of Mallotus roxburghianus in alloxan-induced diabetic rat model. *J. Ethnopharmacol.* 176, 268–280.
- Rubinshtein, D.C., Codogno, P., Levine, B., 2012. Autophagy modulation as a potential therapeutic target for diverse diseases. *Nat. Rev. Drug Discov.* 11 (9), 709–730.
- Sabeur, K., Ball, B., 2007. Characterization of NADPH oxidase 5 in equine testis and spermatozoa. *Reproduction* 134 (2), 263–270.
- Sajad, M., Thakur, S.C., 2020. Insights of Sperm Pathology and its Association with Infertility, Insights of Sperm Pathology and Its Association with Infertility, Innovations In Assisted Reproduction Technology. IntechOpen.
- Sajad, M., Thakur, S.C.J.A.I.M., Biology, pathophysiological risk factors for infertility in women. 155.
- Sajad, M., Thakur, S.C.J.Aih, disease, 2020. Occurrence and bioactivity of phytochemicals and their role in human health. 83.
- Sajad, M., Ahmed, M.M., Thakur, S.C.J.G.R., 2022a. An integrated bioinformatics strategy to elucidate the function of hub genes linked to Alzheimer's disease. 26, 101534.
- Sajad, M., Kumar, R., Thakur, S.C.J.I.N.R., 2022b. History in perspective: the prime pathological players and role of phytochemicals in Alzheimer's disease.
- Sakkas, D., Umer, F., Menezes, Y., Leppens, G., 1993. Effects of glucose and fructose on fertilization, cleavage, and viability of mouse embryos in vitro. *Biol. Reprod.* 49 (6), 1288–1292.
- Salminen, M., Vahlberg, T., Rähilä, I., Niskanen, L., Kivelä, S.L., Irjala, K., 2015. Sex hormones and the risk of type 2 diabetes mellitus: a 9-year follow up among elderly men in Finland. *Geriatr. Gerontol. Int.* 15 (5), 559–564.
- Salvi, R., Castillo, E., Voirol, M.-J., Glauser, M., Rey, J.-P., Gaillard, R.C., Vollenweider, P., Pralong, F.P., 2006. Gonadotropin-releasing hormone-expressing neurons immortalized conditionally are activated by insulin: implication of the mitogen-activated protein kinase pathway. *Endocrinology* 147 (2), 816–826.
- Sangameswaran, B., Jayakar, B., 2008. Anti-diabetic, anti-hyperlipidemic and spermatogenic effects of *Amaranthus spinosus* Linn. on streptozotocin-induced diabetic rats. *J. Nat. Med.* 62 (1), 79–82.
- Sato, S., Kataoka, S., Kimura, A., Mukai, Y., 2016. Azuki bean (*Vigna angularis*) extract reduces oxidative stress and stimulates autophagy in the kidneys of streptozotocin-induced early diabetic rats. *Can. J. Physiol. Pharmacol.* 94 (12), 1298–1303.
- Schoeller, E.L., Schon, S., Moley, K.H., 2012. The effects of type 1 diabetes on the hypothalamic, pituitary and testes axis. *Cell Tissue Res.* 349 (3), 839–847.
- Shalaby, M., Hamowieh, A., 2010. Safety and efficacy of Zingiber officinale roots on fertility of male diabetic rats. *Food Chem. Toxicol.* 48 (10), 2920–2924.
- Shi, G.-J., Li, Z.-M., Zheng, J., Chen, J., Han, X.-X., Wu, J., Li, G.-Y., Chang, Q., Li, Y.-X., Yu, J.-Q., 2017. Diabetes associated with male reproductive system damages: onset of presentation, pathophysiological mechanisms and drug intervention. *Biomed. Pharmacother.* 90, 562–574.
- Skinner, M.K., Griswold, M.D., 1982. Secretion of testicular transferrin by cultured Sertoli cells is regulated by hormones and retinoids. *Biol. Reprod.* 27 (1), 211–221.
- Sm, S., Mahaboob Basha, P., 2017. Fluoride exposure aggravates the testicular damage and sperm quality in diabetic mice: protective role of ginseng and banana. *Biol. Trace Elem. Res.* 177 (2), 331–344.
- Solomon, H., Man, J., Jackson, G., 2003. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart* 89 (3), 251–253.
- Suresh, S., Prakash, S., 2012. Effect of *Mucuna pruriens* (Linn.) on sexual behavior and sperm parameters in streptozotocin-induced diabetic male rat. *J. Sex. Med.* 9 (12), 3066–3078.
- Tesfaye, S., Selvarajah, D., 2012. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. *Diabetes/Metab. Res. Rev.* 28, 8–14.
- Torchinsky, A., Gongadze, M., Orenstein, H., Savion, S., Fein, A., Toder, V., 2004. TNF- $\alpha$  acts to prevent occurrence of malformed fetuses in diabetic mice. *Diabetologia* 47 (1), 132–139.
- Tripathy, D., Dhindsa, S., Garg, R., Khaishagi, A., Syed, T., Dandona, P., 2003. Hypogonadotropic hypogonadism in erectile dysfunction associated with type 2 diabetes mellitus: a common defect? *Metab. Syndr. Relat. Disord.* 1 (1), 75–80.
- Ullisse, S., Jannini, E.A., Pepe, M., De Matteis, S., D'Armiendo, M., 1992. Thyroid hormone stimulates glucose transport and GLUT1 mRNA in rat Sertoli cells. *Mol. Cell. Endocrinol.* 87 (1–3), 131–137.
- Vardi, Y., 2009. Microvascular complications in diabetic erectile dysfunction: do we need other alternatives? *Diabetes Care* 32 (suppl. 2), S420–S422.
- Verma, R., Haldar, C., 2016. Photoperiodic modulation of thyroid hormone receptor (TR- $\alpha$ ), deiodinase-2 (Dio-2) and glucose transporters (GLUT 1 and GLUT 4) expression in testis of adult golden hamster, *Mesocricetus auratus*. *J. Photochem. Photobiol. B: Biol.* 165, 351–358.
- Wabitsch, M., Jensen, B., Blum, P., Christoffersen, W.F., Englaro, C.T., Heinze, P., Rascher, E., Teller, W., Tornqvist, W., Hauner, H., 1996. Insulin and cortisol promote leptin production in cultured human fat cells. *Diabetes* 45 (10), 1435–1438.
- Wang, Y., Zhang, Z., Guo, W., Sun, W., Miao, X., Wu, H., Cong, X., Wintergerst, K.A., Kong, X., Cai, L., 2014. Sulforaphane reduction of testicular apoptotic cell death in diabetic mice is associated with the upregulation of Nrf2 expression and function. *Am. J. Physiol. -Endocrinol. Metab.* 307 (1), E14–E23.
- Zhang, J., Huang, X., Liao, M., Gao, Y., Tan, A., Yang, X., Zhang, H., Mo, L., Zhang, Y., Lu, Z., 2013a. Both total testosterone and sex hormone-binding globulin are independent risk factors for metabolic syndrome: results from Fangchenggang area male health and examination survey in China. *Diabetes/Metab. Res. Rev.* 29 (5), 391–397.
- Zhang, L., Pang, S., Deng, B., Qian, L., Chen, J., Zou, J., Zheng, J., Yang, L., Zhang, C., Chen, X., 2012. High glucose induces renal mesangial cell proliferation and fibronectin expression through JNK/NF- $\kappa$ B/NADPH oxidase/ROS pathway, which is inhibited by resveratrol. *Int. J. Biochem. Cell Biol.* 44 (4), 629–638.
- Zhang, L., Wang, H., Yang, Y., Liu, H., Zhang, Q., Xiang, Q., Ge, R., Su, Z., Huang, Y., 2013b. NGF induces adult stem Leydig cells to proliferate and differentiate during Leydig cell regeneration. *Biochem. Biophys. Res. Commun.* 436 (2), 300–305.
- Zhao, P., Zhou, R., Zhu, X.-Y., Hao, Y.-J., Li, N., Wang, J., Niu, Y., Sun, T., Li, Y.-X., Yu, J.-Q., 2015. Matrine attenuates focal cerebral ischemic injury by improving antioxidant activity and inhibiting apoptosis in mice. *Int. J. Mol. Med.* 36 (3), 633–644.
- Zhao, W., Hu, Y., Long, L.-I., Cai, B., Li, Y.-B., 2020. Protective effects of scutellarin on testicular vessels of rat with type II diabetes mellitus-induced testicular damages. *J. Sun Yat-Sen. Univ.* 260–267.
- Zhao, Y., Tan, Y., Dai, J., Li, B., Guo, L., Cui, J., Wang, G., Shi, X., Zhang, X., Mellen, N., 2011. Exacerbation of diabetes-induced testicular apoptosis by zinc deficiency is most likely associated with oxidative stress, p38 MAPK activation, and p53 activation in mice. *Toxicol. Lett.* 200 (1–2), 100–106.
- Zysk, J., Bushway, A., Whistler, R., Carlton, W., 1975. Temporary sterility produced in male mice by 5-thio-D-glucose. *Reproduction* 45 (1), 69–72.