RESEARCH PAPER

Beyond Glycemic Control: The Polyol Pathway, AGE–RAGE Axis, and Sperm DNA Fragmentation as Drivers of Diabetic Male Infertility

Harsh Rana[1], Avijit Mazumder[2*], Priyanka Bansal[3]

ORCID: 0009-0002-8084-6104 (Harsh Rana) | 0000-0002-3053-8106 (Avijit Mazumder) | 0009-0008-2945-5427 (Priyanka Bansal)

[1] Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park-II, Greater Noida, 201306, Uttar Pradesh, India. Email: harshpundir330@gmail.com

[2*] Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park-II, Greater Noida, 201306, Uttar Pradesh, India. Email: avijitmazum@yahoo.com (Corresponding Author)

[3] Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park-II, Greater Noida, 201306, Uttar Pradesh, India. Email: bansalpriyanka309@gmail.com

Received: 2nd Mar, 2026 | **Revised:** 14th Mar, 2026 | **Accepted:** 4th Apr, 2026 | **Available Online:** 20th Apr, 2026

ABSTRACT

Diabetes mellitus (DM) greatly impacts male reproductive health through hyperglycemia-mediated pathways, which are not adequately addressed by conventional glycemic control. This review integrates current knowledge on the role of the polyol pathway and the advanced glycosylation end-product (AGE)/receptor for AGE (RAGE) pathway in oxidative stress and sperm DNA fragmentation (SDF) in diabetic men. The polyol pathway is hyperactivated by hyperglycemia, leading to NADPH depletion and reactive oxygen species (ROS) accumulation, simultaneously stimulating AGE production that triggers RAGE-mediated oxidative stress. These converging pathways cause testicular dysfunction, sperm damage, and chromatin instability. Evidently, diabetic men have been found to have significantly increased SDF levels even in the presence of normal conventional semen parameters, which correlate with decreased natural conception rates and lower success rates with assisted reproductive technology (ART). The review emphasizes that conventional glycemic control is insufficient to reverse infertility because of the unerasable molecular memory of hyperglycemia-induced molecular alterations. Therapeutic strategies focusing on the pathologic triad of polyol pathway, AGE/RAGE, and oxidative stress have shown promise, including the use of aldose reductase inhibitors, RAGE antagonists, and antioxidants. Dietary and ART strategies, such as testicular sperm extraction in cases with high SDF, also offer hope. This integrated knowledge of diabetes-induced mechanisms of male infertility will help in the development of precision medicine strategies to preserve fertility in diabetic men.

Keywords: Diabetic male infertility, Sperm DNA fragmentation, Polyol pathway, AGE-RAGE axis, Oxidative stress, Epigenetic alterations.

How to cite this article: Rana H, Mazumder A, Bansal P. Beyond Glycemic Control: The Polyol Pathway, AGE–RAGE Axis, and Sperm DNA Fragmentation as Drivers of Diabetic Male Infertility. Int J Drug Deliv Technol. 2026;16(32s):776-793. DOI: 10.25258/ijddt.16.32s.86

Source of support: Nil.

Conflict of interest: The authors declare no conflict of interest.

1. Introduction

Diabetes mellitus (DM) has emerged as a world epidemic with rapid pace and now affects a couple of hundred million adults and projected to further increase in coming decades.[1,2] At the same time, infertility in the male partner accounts for nearly half of all infertile couples worldwide with a decline in semen quality over the decades.[1,3] There is significant overlap between these two disorders, as epidemiological data indicates. The prevalence of DM in those who are infertile is greater than in the general population. Similarly, infertility and subfertility are increasingly recognized as metabolic risk markers for other conditions as well, like diabetes in the future.[3,4] Men with type 1 or type 2 diabetes mellitus (DM) throughout their reproductive years frequently exhibit compromised semen quality

and reduced natural fecundity; moreover, diabetic male partners in assisted reproduction cycles show reduced pregnancy rates compared to non-diabetic controls.[5,6]

A large number of clinical and experimental work now indicates that diabetes has a damaging impact on male reproductive functions. Analysis undertaken by systematic reviews and meta-analyses demonstrated that the sperm quality is adversely impacted in Diabetes Mellitus, particularly type 1 diabetes mellitus. The abnormal morphology, lower volume and reduced progressive motility of sperm is commonly observed in men suffering from DM. Moreover, several studies have indicated an increase in sperm DNA fragmentation, but it may not affect the total sperm count.[5,6] Beyond spermatogenic defects, diabetic men frequently suffer from erectile and ejaculatory dysfunction driven by hypogonadism and structural testicular damage, further compounding fertility challenges.[2,7] Although the findings on routine semen parameters remain heterogeneous, evidence suggest that some diabetic men with subfertility have normal semen profiles. Thus, routine semen analysis might not be sufficient to explain male subfertility or infertility.[5,8]

Conventionally, the management of diabetic complications has focused primarily on glycemic indices such as HbA1c and microvascular outcomes. However, an increasing number of mechanistic evidence indicates that chronic hyperglycemia causes damage of the male reproductive tract through specific biochemical pathways not fully captured by HbA1c levels.[9,10] Under hyperglycemic conditions, glucose is channeled through the polyol pathway, which diminishes sperm motility, abnormal sperm morphology, and compromised membrane and DNA integrity. Consequently, this diverts glucose to sorbitol and fructose depleting NADPH and antioxidant defense system. Most importantly, enhanced production of reactive oxygen species (ROS) emerge that are toxic to sperm [10,11] At the same time, means non-enzymatic glycation that advanced glycation end products AGE accumulates in testis epididymis and semen. The interaction between advanced glycation end-products (AGE) and the receptor for AGE (RAGE) aids in oxidative stress, mitochondrial dysfunction, inflammation, and death in germ cells and supporting cells.[12,13] In diabetic models, high levels of AGEs and RAGE expression are linked with increased DNA fragmentation sperm and chromatin instability.[13]

As spermatozoa is known to be especially sensitive to oxidative and glyco oxidative damage, sperm DNA fragmentation (SDF) can be considered as a more sensitive marker of male reproductive compromise than classical semen parameters. Semen dysfunction is significantly linked to compromised natural conception, diminished efficacy of assisted reproductive technologies, and negative child outcomes, and is persistently elevated in both diabetic men and models, despite occasionally slight variations in concentration or motility.[2,8,9,11] Shifting the focus to SDF then offers a more direct readout of the cumulative action of polyol pathway activation, AGE–RAGE signalling, oxidative stress, mitochondrial injury, and defective DNA repair in the diabetic testis and sperm.

This review integrates clinical and basic science knowledge about infertility in diabetic men, with a particular emphasis on sperm DNA fragmentation. It points out how the polyol pathway and the AGE-RAGE pathway represent the core, hyperglycemia-mediated pathways that link metabolic disturbances to testicular dysfunction and SDF. These pathways result in secondary processes including oxidative stress, mitochondrial impairment, cellular apoptosis, disruptions in the hypothalamic-pituitary-gonadal axis, and unique epigenetic modifications in the male germ cell lineage. The article also discusses the clinical implications of these new understandings about the pathogenesis of infertility in reproductive-age men with diabetes, and it identifies significant gaps in current knowledge, particularly the need for high-quality studies in human subjects that evaluate SDF, pathway-specific biomarkers, and mechanism-based therapies.

2. Diabetes and Male Infertility

According to population-based studies, there is a bidirectional association of diabetes with male infertility. Diabetes prevalence in infertile population ranges from 0.7–1.4% but subfertility is more common in infertile men with diabetes (35-51%) than in general population. Men diagnosed with type 1 diabetes (T1DM) have lower rates of natural fatherhood, especially those with a longer duration of disease. Furthermore, couples with a diabetic male partner assisted reproduction have lower rates of pregnancy.[5,14] Notably, male factor infertility is a predictor for the development of diabetes. Men with oligospermia, azoospermia, and aspermia have a significantly increased risk of developing diabetes, suggesting a common pathophysiological link.[15] Mendelian randomization experiments employing large-scale genome-wide association study data have revealed that

genetically predicted type 2 diabetes (T2DM) has a clear association with erectile dysfunction and male infertility. These findings establish diabetes as an etiological factor rather than a mere associative comorbidity.[12,14,16]

2.1) Effect of diabetes mellitus on Conventional Semen Parameters

Systematic reviews and meta-analyses have shown diabetes-related changes in conventional semen parameters. A meta-analysis including 21 studies (1,218 diabetic men vs. 1,171 controls) showed a significant reduction in semen volume, sperm concentration, total and progressive motility, and normal morphology in diabetic men, with an unchanged total sperm count.[17] Similar results were obtained in studies combining obesity and diabetes, showing a reduction in semen volume, sperm count, concentration, and progressive motility, with decreased testosterone levels.[18]

There are differences observed when comparing type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). In T1DM, meta-analyses encompassing 380 patients and 434 controls indicated a substantial reduction in progressive motility and normal morphology, with a tendency towards lower semen volume, but an unaltered total sperm count and concentration.[6] Conversely, T2DM is characterized by a systemic inflammatory/oxidative state with reduced sperm vitality and increased DNA damage (Table 1).[10,11] These differences are due to the pathophysiological mechanisms underlying these conditions, where T1DM mainly affects mitochondrial function and epididymal emptying, and T2DM is driven by insulin resistance-related inflammation and oxidative stress .[13,19] These distinct pathophysiological mechanisms underscore the need for differential diagnostic approaches.

2.2) Beyond Standard Analysis: Sperm DNA Fragmentation and Functional Markers

Standard semen analysis often fails to recognize the reproductive risk associated with diabetes, as some diabetic men have normal semen parameters despite reduced fertility potential. Meta-analytic data clearly show that diabetic men have significantly increased sperm DNA fragmentation (SDF) even when total sperm count is in the normal range.[5,17] Comparative studies demonstrate that type 2 diabetes mellitus (T2DM) is specifically associated with increased SDF and reduced sperm vitality, whereas type 1 diabetes mellitus (T1DM) shows more severe mitochondrial damage and impaired motility.[19]

Mechanistically, diabetes is associated with oxidative damage, mitochondrial damage, and AGE-RAGE-mediated injury, resulting in sperm DNA breaks, aberrant chromatin structure, and loss of mitochondrial membrane potential.[9,13,20] Both human and animal studies suggest that T1DM is associated with reduced mitochondrial membrane potential and mtDNA damage, whereas T2DM focuses on inflammatory oxidative stress with concomitant increased SDF.[13,19,20]

Clinically, high SDF significantly affects reproductive success. Meta-analyses of IVF/ICSI cycles have shown that high SDF reduces implantation and pregnancy success, especially in conventional IVF, with detrimental effects on live birth rate.[21–23] Recent cohort studies (870 ICSI single-blastocyst cycles) have shown that each 1% increase in SDF reduces the probability of high fertilization rates and excellent-quality blastocyst development, indicating embryonic dysfunction.[24] Furthermore, high SDF is associated with recurrent pregnancy loss and implantation failure, and meta-analytic data indicate improved clinical pregnancy and live birth rates when testicular sperm with lower DNA damage is used in ICSI cycles.[21,25]

In conclusion, the clinical data clearly show that diabetes has profound impacts on male fertility potential through SDF, mitochondrial damage, and vitality defects, which are only incompletely reflected by standard semen analysis.

3. Hyperglycemia-Driven Pathways in the Testis and Epididymis

Hyperglycemia causes testicular and epididymal damage through multiple, interrelated biochemical pathways that culminate in oxidative stress and inflammation (Figure 1).

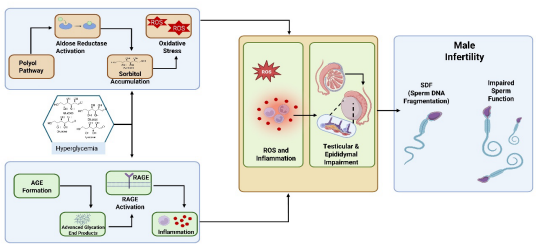

Figure 1. Hyperglycemia-driven pathogenic cascade in diabetic male infertility. Chronic hyperglycemia activates the **polyol pathway** (depleting NADPH/GSH) and the **AGE-RAGE axis**. These converging mechanisms generate excessive ROS,

causing testicular and epididymal impairment, mitochondrial dysfunction, and sperm DNA fragmentation (SDF), ultimately leading to impaired sperm function.

3.1) Major hyperglycemia-driven pathways

The polyol pathway and protein-kinase c (PKC) pathway are overactivated in diabetic testes to metabolize excess glucose. Hyperglycemia enhances aldose reductase-mediated glucose-sorbitol and glucose-fructose production and activates diacylglycerol-PKC signaling, both of which are increasingly activated in type 1 diabetic mouse testes.[9,11,26] These pathways enhance redox imbalance, reactive oxygen species production, and spermatogenic disruption.[26,27]

At the same time, hyperglycemia accelerates non-enzymatic glycation and the formation of advanced glycosylation end-products (AGEs). Methylglyoxal and AGE-carboxymethyl lysine are increased in diabetic testes and epididymides, and the AGE receptor (RAGE) is widely expressed in testicular tissues.[28–30] AGEs/RAGE signaling pathways are involved in Leydig cell steroidogenic dysfunction, endoplasmic reticulum (ER) stress, and apoptosis, further impairing testosterone secretion and spermatogenesis.[29,30]

Hyperglycemia also enhances mitochondrial overload and parallel glucose metabolism (PKC, polyol, hexosamine, and AGEs) pathways, which cumulatively enhance mitochondrial reactive oxygen species production and activate pro-inflammatory pathways, including NF-κB, NLRP3 inflammasome, and endoplasmic reticulum (ER) stress signaling in testicular cells. [8–10,31]

3.2) Effects on the testis and epididymis

These pathways affect the hypothalamic-pituitary-gonadal axis, leading to decreased GnRH, LH/FSH signaling, and testosterone, culminating in hypogonadism in diabetic men. [8,9,11] In the testis, hyperglycemia-induced oxidative stress and inflammation cause Leydig cell injury (reduced steroid secretion, mitochondrial disorganization, and increased apoptosis) and Sertoli cell injury (vacuolization, impaired metabolic support for germ cells).[31–33] Blood-testis barrier tight junction proteins are reduced, impairing barrier function and germ cell migration.[32]

In the epididymis, diabetes creates a pro-oxidative and low-antioxidant environment: mitochondrial regulators (SIRT1/PGC-1α/SIRT3) and complexes are reduced, antioxidant enzymes (SOD, CAT, GPx) are decreased, but protein nitration and lipid peroxidation are increased. This environment promotes sperm DNA fragmentation and abnormalities in maturation.[32,34]

3.3) Oxidative stress as the central hub

Oxidative stress is the central mechanism in these tissues. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced by hyperglycemia-induced mitochondrial dysfunction, NADPH oxidase activation, polyol pathway-mediated NADPH depletion, and AGE-RAGE signaling.[26,28] Lipid peroxidation is increased in the testis of diabetic models, and antioxidant defenses are reduced. Activation of inflammatory mediators (NF-κB, NLRP3) and apoptosis are increased in germ, Sertoli, and Leydig cells, associated with impaired spermatogenesis and abnormal sperm morphology and motility.[35,36]

Spermatozoa are highly vulnerable: their membranes are rich in polyunsaturated fatty acids, and their cytoplasm lacks antioxidant enzymes and DNA repair mechanisms.[34,37] Diabetic animals show increased 4-HNE adducts in sperm, mitochondrial dysfunction, ATP depletion, and increased DNA fragmentation and chromatin abnormalities, directly linking oxidative damage to impaired motility and fertility.[34,38,39]

In conclusion, hyperglycemia activates the polyol pathway, protein-kinase C (PKC), and AGE/RAGE signaling in the testis, generates a pro-oxidative and pro-inflammatory microenvironment in the testis and epididymis, and, through ROS-mediated injury to somatic cells, barrier components, and sperm, causes diabetic male infertility.

Table 1: Clinical studies linking diabetes types to semen parameters and sperm DNA fragmentation, highlighting distinct pathophysiological mechanisms.

S. no	Population (n)	Diabetes Type	Key Semen Findings	SDF (%)	Clinical Relevance	References
1	93 diabetic men (38 DM1, 55 DM2), 100	DM1, DM2	DM 2: increased oxidative stress, decrease	Increased in DM2; not specified for DM1	Different pathophysiological mechanisms in DM1	[19]

	controls		d sperm vitality; DM1: low ejaculate volume, decreased motility		and DM2 contribute to male infertility; monitoring seminal parameters recommended	
2	380 DM1 men, 434 controls	DM1	Lower normal morphology and progressive motility; trend to lower volume; total count unchanged	Data on SDF too few	DM1 impairs semen quality and fertility potential; need for comprehensive hormonal and seminal evaluation	[6]
4	Diabetic men undergoing ART	Mixed/unspecified	Lower progressive motility; high	37% vs. 21% in non-diabetics	Increased sperm DNA damage linked to	[95]
			er nuclear DNA fragmentation		poor embryonic development and pregnancy outcomes in diabetic patients undergoing ART	
5	30 diabetic, 30 controls	Mixed/unspecified	Decreased motility, concentration, increased morphological abnormalities	Increased DNA/chromatin damage	Diabetes affects sperm maturation and chromatin integrity beyond routine semen analysis	[96]
6	Review of multiple small studies	DM1, DM2	Negative effect on morphology and motility; contradictory results on	Not consistently reported	Diabetes impairs male reproductive health and couple fertility; larger detailed studie	[5]

			other parameters		s needed	
7	726 primary infertile men	Insulin resistance marker related to diabetes risk	Worse sperm concentration and hormonal profile in men with insulin resistance	Higher risk of SDF >30 % with IR marker	Insulin resistance correlates with worse semen parameters and higher sperm DNA fragmentation in infertile men	[97]
8	Streptozotocin-induced T1D rats	T1D model	Reduced sperm count, viability, motility; increased DNA fragmentation	Increased but % not specified	T1D-induced oxidative stress disrupts microtubule dynamics affecting sperm quality	[38]
9	Review article	DM overall	Reduced motility, abnormal morphology	Increased SDF reported	Oxidative stress from diabetes damages sperm	[11]
			linked to oxidative stress		DNA and impairs fertility	

4. The Polyol Pathway in Diabetic Testis and Sperm

The polyol pathway plays an important role in glucose regulation in hyperglycemic conditions and is a major mechanism of oxidative stress-mediated damage to the male reproductive organs.

4.1) Core biochemistry of the polyol pathway

The pathway consists of two enzyme-catalyzed reactions: the reduction of glucose to sorbitol by aldose reductase (AR) using NADPH, and the oxidation of sorbitol to fructose by sorbitol dehydrogenase (SDH) with the concomitant reduction of NAD^+ to NADH.[11,40,41] In diabetic conditions, as much as 30% of glucose is shunted through this pathway, resulting in the depletion of NADPH and accumulation of NADH, thereby disrupting the redox couples NADPH/$NADP^+$ and NADH/NAD^+, and enhancing the production of reactive oxygen species (ROS).[40–42]

4.2) Expression of the polyol pathway in the testis

The testis expresses both AR and SDH, with AR being predominantly localized in Sertoli cells and SDH in germ cells, suggesting a physiological role for this pathway in glucose handling and fructose synthesis for energy utilization by sperm cells. However, in diabetic conditions, the testicular sorbitol levels are substantially elevated (by 1.7-fold in Ins2Akita mice at 24 weeks), indicating the activation of the polyol pathway specifically in the testis, but not in the epididymis. [9]

4.3) Mechanisms of polyol activation-induced testicular damage and sperm abnormalities

Activation of the polyol pathway by hyperglycemia in diabetes leads to testicular oxidative stress through several mechanisms:

- **NADPH Depletion:** Depletion of NADPH inhibits glutathione reductase function and reduced glutathione regeneration, reducing the antioxidant capacity.[11,40,41]
- **Excess NADH:** promotes mitochondrial and NADH oxidase-mediated superoxide production.[40,41]
- **Fructose Accumulation:** The generated fructose from sorbitol can be further

converted into other reactive glycating compounds, which accumulate advanced glycosylation end-products (AGEs) and trigger more ROS production.[41]

These oxidative injuries cause damage to testicular cells and sperm, leading to decreased motility, morphological abnormalities, increased DNA fragmentation, and disrupted membrane integrity in diabetic men.[11]. Experimental diabetic models have shown increased testicular oxidative injury and impaired spermatogenesis, which are associated with polyol pathway activation and sorbitol accumulation.[9,43]

4.4) Therapeutic approaches

Agents that inhibit AR/SDH activity or polyol transport in the testis, such as sulfated or plant-derived polysaccharides, honokiol, and magnolol, can inhibit aldose reductase and polyol dehydrogenase enzyme activities, enhance antioxidant defenses, and partially correct diabetic testicular injury and sperm abnormalities.[43–45]

5. AGE–RAGE Axis and Sperm DNA Fragmentation

In hyperglycemic and high AGE conditions, the AGE-RAGE pathway is a major upstream mediator of sperm DNA damage. The detailed molecular mechanisms of the polyol pathway and AGE-RAGE crosstalk are presented in (Figure 2), which shows how these pathways converge to cause sperm damage through multiple interconnected mechanisms

5.1) Mechanisms of AGE-RAGE pathway activation

Advanced glycosylation end-products (AGEs) are formed by the non-enzymatic glycation of proteins, lipids, and nucleic acids, and their buildup has been found in diabetes, obesity, and diseases linked with an AGE-rich diet.[46,47] The primary receptor for AGEs, RAGE, is a cell surface-bound immunoglobulin-like receptor whose activation initiates NADPH oxidase, mitogen-activated protein kinases (MAPKs), and nuclear factor κB (NF-κB), thereby enhancing oxidative stress and inflammatory reactions.[46,48,49] RAGE and AGEs are expressed throughout the male reproductive system, including the testis, epididymis, and sperm, and their expression is elevated in diabetic males and in animal models of diabetes.[50–52]

5.2) Sperm RAGE expression and its implications for DNA susceptibility

In human sperm, RAGE expression is predominantly restricted to the acrosomal cap and the equatorial segment of the sperm head, areas that overlie the nucleus and are subject to extensive remodeling during epididymal maturation.[53,54] This pattern of expression places ligand-receptor complexes near nuclear DNA and may compromise the integrity of the plasma membrane barrier, thus facilitate reactive oxygen species (ROS) entry and allow direct AGE/RAGE-mediated damage to chromatin-associated proteins.[54,55]

5.3) Mechanistic connection between AGE-RAGE activation and sperm DNA fragmentation

Cumulative evidence from both human cohorts and animal models establishes a strong mechanistic link between AGE-RAGE activation and sperm DNA fragmentation, with RAGE expression correlating strongly ($r \approx 0.81$) with TUNEL-positive fragmentation (Table 2):

- Mice fed an AGE-diet show increased testicular AGE (CML) levels, RAGE expression, reduced antioxidant activity, and increased sperm DNA fragmentation, along with protamine deficiency and residual histones, indicating AGE/RAGE-mediated oxidative and chromatin damage.[47]
- High membrane-bound RAGE expression in sperm is linked to increased oxidative DNA damage (8-OHdG) and DNA fragmentation in non-diabetic men, along with decreased motility, mitochondrial membrane potential, and increased apoptosis. This suggests that sperm labeled with RAGE represent an intrinsically damaged and ROS-dysfunctional subset.[53]
- High sperm RAGE expression is strongly associated with DNA fragmentation, according to a meta-analysis of diabetic semen. This is likely because the AGE-RAGE pathway produces too many reactive oxygen species (ROS), which break DNA strands.[55]
- Diabetic patients have increased RAGE protein expression and significantly higher sperm DNA fragmentation, with a very strong positive correlation between RAGE expression and TUNEL-positive fragmentation ($r \approx 0.81$).[56]

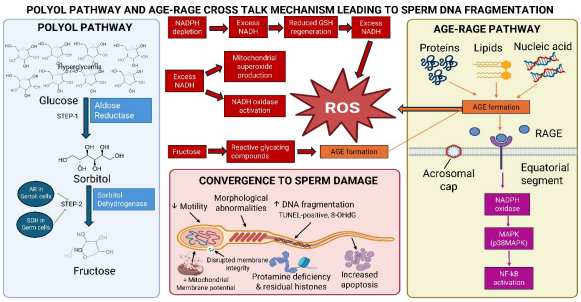

Figure 2. Molecular crosstalk between polyol and AGE-RAGE pathways leading to sperm damage. Detailed schematic illustrating how aldose reductase activity and AGE formation synergistically amplify ROS production via mitochondrial superoxide and NADPH oxidase activation. This oxidative burst directly damages sperm chromatin (increasing 8-OHdG and strand breaks), disrupts protamine packaging, and induces apoptosis, compromising fertilization potential.

5.4) Experimental blockade of AGE-RAGE

Blocking AGE-RAGE provides further evidence for its causal role:

- In type 2 diabetes mellitus (T2DM) mice, a DNA aptamer targeting AGEs decreases testicular AGE levels, macrophage infiltration, apoptosis, and oxidative stress, and improves sperm count, motility, and viability, despite the absence of changes in blood glucose levels, suggesting a local AGE-RAGE-mediated oxidative insult.[57]
- Various interventions using small molecules or phytochemicals that inhibit AGEs/RAGE and downstream signaling molecules such as Nox4, p38MAPK, and NF-κB reduce testicular oxidative stress and apoptosis and improve sperm parameters and DNA fragmentation index in diabetic models.[52,58,59]
- **Table 2:** Evidence linking AGE-RAGE activation to sperm DNA fragmentation across human and animal models. Key findings include strong RAGE-SDF correlation ($r \approx 0.81$), chromatin defects, and impaired spermatogenesis. Therapeutic blockade (e.g., aptamers, catalpol) mitigates damage independent of glycemic control, highlighting direct therapeutic potential.

Model / pop	Tissue or fluid (AGE)	Main AGE/RAGE findings	Sperm DNA fragmentation	Fertility-related endpoints (semen, testis, clinical)	Citations
Diabetic men vs. controls	Testis/epididymis/sperm/seminal plasma	RAGE ↑ in testis/epididymis; acrosomal sperm RAGE; ↑ seminal plasma/sperm RAGE in diabetics	↑ SDF in diabetics; AGEs proposed contributor	Oxidative stress link: role in diabetic infertility (pregnancy not assessed)	51, 54–56
Diabetic men vs. controls	Sperm (membrane RAGE)	↑ Sperm RAGE protein in diabetics	↑ SDF (TUNEL); strong RAGE-SDF correlation (r≈0.81)	RAGE central to diabetic sperm dysfunction; DNA damage implies ↓ fertility	55, 56
Non-diabetic, non-obese, non-smoking men	Sperm membrane RAGE	RAGE on acrosomal/equatorial regions; marks damaged subpopulation	RAGE⁺ sperm: ↑ TUNEL, ↑ 8-OHdG vs. RAGE⁻	RAGE⁺: ↓ motility, ↑ apoptosis, ↓ fertilizing potential	53
C57BL/6 mice, AGE-diet vs.	Testis/sperm (CML/RAGE)	AGE diet: ↑ CML/RAGE; ↓ antioxidants	↑ SDF; chromatin defects (protamine/histone)	↓ Count/motility; ↑ abnormalities; AGE/RAGE → subfertility	47

control					
BALB/c mice & SD rats, AGE-diet ± inhibitor	Testis/epididymal sperm (RAGE/MDA)	AGE diet: ↑ RAGE/MDA; silymarin normalizes	SDF not measured; oxidative stress suggests genomic risk	↓ Count, ↑ abnormalities; silymarin restores	[53,98]
KK-Ay T2D mice ± AGE aptamer	Testis/epididymal sperm (AGEs/RAGE)	Early AGEs → ↑ RAGE; aptamer ↓ RAGE/oxidative stress/inflammation	8-OHdG ↑ (↓ by aptamer); SDF inferred	Diabetes: ↓ sperm quality; aptamer reverses (glycemia unchanged)	[57]
KK-Ay diabetic mice ± catalpol	Testis/GC-2 cells (AGEs/RAGE/Nox4)	Diabetes: ↑ RAGE/Nox4/NF-κB; catalpol suppresses	AGEs → ROS/apoptosis; catalpol protective (SDF not quantified)	Catalpol: ↑ histology, hormones, ↓ oxidative stress/apoptosis; improves fertility	[58]
STZ-diabetic rats vs. controls	Testis/epididymal sperm (AGE/RAGE/MAPKs)	Diabetes: ↔ AGE/RAGE; ↑ JNK/p38/caspase-3; ↓ catalase, ↑ MDA	SDF not measured; apoptosis/oxidative stress suggest damage	↓ Progressive motility; AGE/RAGE pathways impair function	[50,99]
Oligoasthenozoospermic men (observational)	Serum AGEs/inhibin B (Sertoli)	↑ Serum AGEs, ↓ inhibin B; AGE diet → Sertoli senescence (mice)	SDF not measured; Sertoli stress suggests genomic risk	↓ Count, ↑ abnormalities; silymarin restores spermatogenesis; omega-3 rescues; AGE/RAGE → infertility risk	[47,100]

6. Sperm DNA Fragmentation: Mechanisms, Measurement, and Clinical Relevance

Sperm DNA fragmentation (SDF) refers to the breaks or oxidative damage in the paternal genome and is increasingly recognized as a key aspect of male-factor infertility [60].

6.1) Mechanisms of Sperm DNA Fragmentation

The key biological mechanisms involved in DNA fragmentation are:

Chromatin packaging defects: Incomplete histone substitution by protamines and impaired topoisomerase programmed nicks during spermiogenesis make DNA vulnerable to damage.[23,61,62]

Abortive apoptosis: Insufficient elimination of defective germ cells allows caspase- and endonuclease-mediated DNA-damaged sperm to be released.[22,61]

Oxidative stress: Excessive ROS production by leukocytes, varicocele, infection, heat, lifestyle, and diabetic mechanisms (polyol and AGE-RAGE) cause single- and double-strand breaks and oxidized bases like 8-OHdG.[22,63,64]

Post-testicular events: Damage may accumulate during epididymal transport, ejaculation, in vitro manipulation, and cryopreservation, which could increase SDF.

6.2) Measurement: Main Assays and Performance

Commonly used assays differ significantly in their operating principles, sensitivity to specific types of DNA damage, and clinical predictive value for fertility outcomes **(Table 3)**.

Table 3: Comparative overview of sperm DNA fragmentation assays, detailing their principles, clinical predictive value for fertility outcomes, and supporting literature.

Assay	Principle / features	Clinical notes	Citations
TUNEL	Labels DNA strand breaks in situ	Fair prediction of IVF/ICSI	[22,69,101]

		pregnancy (AUC≈0.71) widely used	
Comet (alkaline)	Single-cell gel electrophoresis; tail reflects breaks	Good discrimination of fertile vs infertile; AUC≈0.73 in MAR meta-analysis	63,69,101
SCSA	Flow-cytometric acridine orange (denaturation susceptibility)	Best standardized; predicts infertility but weaker MAR prediction in some reviews	22,63,69
SCD test	Halo formation around sperm head	Technically simple; modest predictive value in MAR	64,69

6.3) Clinical Relevance

Epidemiological and mechanistic evidence links increased SDF to:

- **Semen quality**: Poorer semen quality is associated with higher DNA fragmentation index (DFI) values, which are reflected in lower concentration, motility, and normal morphology.[23,65]
- **Natural conception and IUI**: Higher SDF values are associated with lower chances of natural conception and IUI success.[64,66,67]
- **IVF/ICSI success rates**: Higher SDF values are related with decreased rates of fertilization success, embryo quality, pregnancy rates, live birth rates, and higher miscarriage rates in several studies, however the size of relationship and threshold values range.[23,64–66,68]
- **ART prognostic tests:** In a major meta-analysis, the ability of TUNEL and Comet assays to predict ongoing pregnancy after IVF/ICSI was found to be only moderately accurate, while the accuracy of SCSA and SCD was found to be poor; however, these tests have reasonable sensitivity but poor specificity, thus precluding their use as prognostic tests in routine clinical practice.[69]

Current guidelines and SWOT analysis-based reviews suggest that SDF testing has a potential role in selected situations such as varicocele, idiopathic/unexplained infertility, recurrent pregnancy loss, and repeated ART failure, but not in routine testing of all couples due to heterogeneity of tests, lack of universally accepted thresholds, and a paucity of high-quality data on outcome studies.[22,70–74]

7. Epigenetic and Transgenerational Aspects

Besides direct DNA strand breaks, hyperglycemia also reprograms the sperm epigenome by oxidative stress-mediated mechanisms. Men with type 2 diabetes mellitus (T2DM) have hundreds to thousands of differentially methylated CpG sites in their sperm compared with BMI-matched controls, with a strong bias toward hypermethylation at loci essential for development.[75–77] Type 1 diabetes mellitus (T1DM) also impacts approximately 13% of arrayed CpGs, which are enriched in immune and metabolic functions.[78] Importantly, imprinting control regions demonstrate locus-specific dysregulation: H19 and MEST differentially methylated regions (DMRs) are hypomethylated, whereas SNRPN is hypermethylated in diabetic men with abnormal semen parameters, suggesting impaired germline epigenetic integrity.[79,80]

Simultaneously, chromatin remodeling is also impaired. Hyperglycemia impairs histone-protamine exchange during spermiogenesis, with reduced transition proteins and protamines and aberrantly exposed nucleosomal DNA.[81,82] In T1DM mouse models, sustained changes in the protamine 1/2 ratio over two generations are associated with enhanced DNA fragmentation and reduced fertility.[83] Simultaneously, diabetes also disturbs testicular microRNA (miRNA) expression profiles, with consistent impairment of miRNAs regulating insulin signaling, inflammation, and apoptosis.[13,82,84]

These epigenetic lesions are functional. Paternal prediabetes in mice causes sperm methylation differences that significantly overlap with genes that are differentially methylated in offspring pancreatic islets, including Pik3ca and Pik3r1 loci that show partial resistance to post-fertilization demethylation, thus connecting paternal metabolic disease to offspring β-cell dysfunction.[13,84,85] Paternal T1DM or T2DM exposure causes intergenerational subfertility, as

evidenced by decreased sperm numbers, increased apoptosis, and persistent changes in testicular gene expression in F1 and F2 male offspring.[83,85]

Mechanistically, oxidative lesions such as 8-OHdG are the key to connecting DNA fragmentation to epimutations.[86] ROS produced through polyol flux and AGE-RAGE signaling cause strand breaks and impair DNA methyltransferase function simultaneously, while impairing protamine incorporation. This two-hit damage causes diabetic male infertility to transition from an ejaculate quality problem to a germline epigenetic disease, with environmentally stable, persistent epigenetic marks that may evade reprogramming in offspring and shape offspring metabolic health across generations.

8. Therapeutic and Clinical Implications

Glycemic optimization diminishes polyol transport and advanced glycosylation end-product (AGE) formation but does not completely correct sperm DNA fragmentation (SDF), suggesting an irreversible molecular signature from previous hyperglycemia. [8,11,13] In diabetic animal models, metformin provides a dual action: in addition to its glucose-lowering effects, it inhibits aldose reductase activity, increases testicular insulin sensitivity, and significantly reduces SDF while improving sperm motility and testosterone secretion. [87] Human studies examining the direct relationship between HbA1c reduction and SDF improvement are scarce; however, systematic reviews demonstrate that poor metabolic control is associated with increased levels of oxidative stress biomarkers and decreased semen quality.[5,11,88] Drug-class effects are worth mentioning sulfonylureas and thiazolidinediones can decrease sperm vitality in selected populations, whereas GLP-1 receptor agonists demonstrate potential in preclinical studies for reducing testicular AGE deposition.[8,13,89] Early metabolic therapy, before the onset of chronic hyperglycemia, likely provides the greatest reproductive benefit. Aldose reductase inhibitors decrease sorbitol accumulation and NADPH depletion in the diabetic testis, thus maintaining glutathione stores in animal models; human reproductive outcomes are undefined. RAGE and AGE inhibitors decrease NF-κB activation and testicular inflammation in rodents, partially correcting spermatogenesis.[8,11,13]

8.1) Lifestyle optimization as a first-line therapeutic strategy

Lifestyle modifications have remained an essential component for improving semen quality and decreasing sperm DNA fragmentation (SDF) in diabetic or metabolically active men. Organized interventions that include weight loss, regular exercise, improved dietary habits (especially the Mediterranean diet with high antioxidant intake), smoking cessation, and avoidance of testicular heat exposure have shown small but significant benefits in terms of sperm motility, morphology, and DNA integrity.[60,90,91] The results of meta-analyses suggest that lifestyle modification can decrease SDF by 3% in a three-month period, making it an easily available adjunct therapy.[91] Non-pharmacologic approaches, such as yoga, may also improve mitochondrial activity and antioxidant potential, providing additional protection against sperm DNA damage from oxidative stress.[92]

8.2) Diagnostic and assisted reproductive technology (ART) recommendations

Sperm DNA fragmentation (SDF) analysis is being increasingly recommended in diabetic males with unexplained infertility, recurrent pregnancy loss, failure of assisted reproductive technology (ART), or related metabolic condition. Management according to guidelines should be individualized based on the SDF index: high SDF index requires more aggressive glycemic control and lifestyle modification, along with specific antioxidant therapy, despite the lack of robust evidence to support the routine use of antioxidants.[37,73] It is important to exercise caution when interpreting the results in diabetic patients owing to the absence of direct evidence, but ART can be considered in relation to the timing of intracytoplasmic sperm injection (ICSI) or, in certain cases with severely fragmented ejaculated sperm DNA, testicular sperm retrieval, which has improved outcomes in infertility resulting from oxidative stress.[73,93,94]

9. Conclusions

This review lifts the veil on the impact of diabetes mellitus on male fertility, focusing on the role of sperm DNA fragmentation (SDF) as a major biomarker. It emphasizes two major pathways mediated by hyperglycemia: the polyol pathway and the AGE-RAGE pathway. Both pathways contribute to oxidative damage, mitochondrial dysfunction, and epigenetics in the male germline, making it difficult for sperm to be of high quality. This has significant implications for conception and assisted reproductive technology. Notably, just managing glucose levels will not reverse the process because some molecular “scars” from previous hyperglycemia remain in the system. There is evidence for a multi-step approach: first, manage

metabolic problems, and then specifically target the offending pathways (e.g., using aldose reductase inhibitors or RAGE antagonists), and finally incorporate antioxidants and lifestyle modifications. SDF analysis should be considered in diabetic men with idiopathic infertility or recurrent pregnancy loss. In diabetic men with high SDF in ejaculated sperm (>40%), testicular sperm extraction may be beneficial. Future studies should focus on identifying pathway-specific biomarkers and therapies and validating them in high-quality human studies. In the end, incorporating reproductive health into diabetes care is critical for sustaining fertility potential in diabetic males, with substantial consequences for quality of life and reproductive planning.

Acknowledgment

The authors express their sincere gratitude to the Department of Pharmacy, Noida Institute of Engineering and Technology, India, for providing valuable academic and research support during the preparation of this manuscript.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval. **Informed Consent Statement**

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not applicable.

Author Contributions

Harsh Rana: Methodology, Writing – Review & Editing; Priyanka Bansal: Data Collection, Analysis, Review & Editing; Avijit Mazumder: Visualization, Supervision.

References

1. Temidayo So, Stefan SP. Diabetes mellitus and male infertility. Asian Pacific Journal of Reproduction. 2018;7(1):6–14. doi:10.4103/2305-0500.220978
2. HE Z, YIN G, LI QQ, ZENG Q, DUAN J. Diabetes Mellitus Causes Male Reproductive Dysfunction: A Review of the Evidence and Mechanisms. In Vivo (Brooklyn). 2021 Aug 17;35(5):2503–11. doi:10.21873/invivo.12531
3. Graziani A, Scafa R, Grande G, Ferlin A. Diabetes and male fertility disorders. Mol Aspects Med. 2024 Oct;99:101303. doi:10.1016/j.mam.2024.101303
4. Kaltsas A, Koumenis A, Stavropoulos M, Kratiras Z, Deligiannis D, Adamos K, et al. Male Infertility and Reduced Life Expectancy: Epidemiology, Mechanisms, and Clinical Implications. J Clin Med. 2025 Jun;14:3930. doi:10.3390/jcm14113930
5. Lotti F, Maggi M. Effects of diabetes mellitus on sperm quality and fertility outcomes: Clinical evidence. Andrology. 2022;11:399–416. doi:10.1111/andr.13342
6. Facondo P, Di Lodovico E, Delbarba A, Anelli V, Pezzaioli L, Filippini E, et al. The impact of diabetes mellitus type 1 on male fertility: Systematic review and meta-analysis. Andrology. 2021;10:426–40. doi:10.1111/andr.13140
7. Jangid T, Jain A, Bhardwaj GS, Jangir R, Jain GC. Diabetes mellitus-induced disruptions of male reproductive functions: A comprehensive review. Asian Pacific Journal of Reproduction. 2025. doi:10.4103/apjr.apjr_214_25
8. Zhang W, Tong L, Jin B, Sun D. Diabetic testicular dysfunction and spermatogenesis impairment: mechanisms and therapeutic prospects. Front Endocrinol (Lausanne). 2025;16. doi:10.3389/fendo.2025.1653975
9. Maresch C, Stute D, Alves M, Oliveira P, De Kretser D, Linn T. Diabetes-induced hyperglycemia impairs male reproductive function: a systematic review. Hum Reprod Update. 2017;24(1):86–105. doi:10.1093/humupd/dmx033
10. Barkabi-Zanjani S, Ghorbanzadeh V, Aslani M, GhalibafSabbaghi A, Chodari L. Diabetes mellitus and the impairment of male reproductive function: Possible signaling pathways. Diabetes Metab Syndr. 2020;14 5:1307–14. doi:10.1016/j.dsx.2020.07.031
11. Dena SM, Adeleye AO, Mohlala K, Langa BC, Opuwari C. The Impact of Diabetes Mellitus-Related Oxidative Stress on Male Fertility: A

Review. J Diabetes. 2025;17. doi:10.1111/1753-0407.70157

12. Huang R, Chen J, Guo B, Jiang C, Sun W. Diabetes-induced male infertility: potential mechanisms and treatment options. Molecular Medicine. 2024;30. doi:10.1186/s10020-023-00771-x
13. Rong J, Leng X, Jiang K, Tan J, Dong M. Systemic impacts of diabetes on spermatogenesis and intervention strategies: multilayered mechanism analysis and cutting-edge therapeutic approaches. Reprod Biol Endocrinol. 2025;23. doi:10.1186/s12958-025-01454-4
14. Fan C, Zhang J, Qiu D. Causal relationship between genetically predicted type 2 diabetes mellitus and male infertility. Front Endocrinol (Lausanne). 2024;15. doi:10.3389/fendo.2024.1357279
15. Glazer C, Bonde J, Giwercman A, Vassard D, Pinborg A, Schmidt L, et al. Risk of diabetes according to male factor infertility: a register-based cohort study. Hum Reprod. 2017;32:1474–81. doi:10.1093/humrep/dex097
16. Zhu XB, Niu ZH, Fan WM, Sheng CS, Chen Q. Type 2 diabetes mellitus and the risk of male infertility: a Mendelian randomization study. Front Endocrinol (Lausanne). 2023;14. doi:10.3389/fendo.2023.1279058
17. Zhu JZ, Dong XY, Liang J, Zhang Z, Hu XY, Li L. Effects of diabetes mellitus on semen quality in adult men : a systematic review and meta-analysis. Int J Clin Exp Med [Internet]. 2017 Jan [cited 2026 Feb 28];10:11290–303. Available from: https://www.researchgate.net/publication/319501261_Effects_of_diabetes_mellitus_on_semen_quality_in_adult_men_A_systematic_review_and_meta-analysis
18. Zhong O, Ji L, Wang J, Lei X, Huang H. Association of diabetes and obesity with sperm parameters and testosterone levels: a meta-analysis. Diabetol Metab Syndr. 2021 Oct;13. doi:10.1186/s13098-021-00728-2
19. Condorelli R, La Vignera S, Mongioì L, Alamo A, Calogero A. Diabetes Mellitus and Infertility: Different Pathophysiological Effects in Type 1 and Type 2 on Sperm Function. Front Endocrinol (Lausanne). 2018;9. doi:10.3389/fendo.2018.00268
20. Hao Y, Yang Z, Feng Y, Zhao Y, Ren Y. Inflammation-mediated effects of diabetes mellitus on male fertility: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2025;16. doi:10.3389/fendo.2025.1600565
21. Ribas-Maynou J, Yeste M, Becerra-Tomás N, Aston K, James E, Salas-Huetos A. Clinical implications of sperm DNA damage in IVF and ICSI: updated systematic review and meta-analysis. Biological Reviews. 2021;96(4):1284–300. doi:10.1111/brv.12700
22. Farkouh A, Salvio G, Kuroda S, Saleh R, Vogiatzi P, Agarwal A. Sperm DNA integrity and male infertility: a narrative review and guide for the reproductive physicians. Transl Androl Urol. 2022;11:1023–44. doi:10.21037/tau-22-149
23. Stavros S, Potiris A, Molopodi E, Mavrogianni D, Zikopoulos A, Louis K, et al. Sperm DNA Fragmentation: Unraveling Its Imperative Impact on Male Infertility Based on Recent Evidence. Int J Mol Sci. 2024;25:10167. doi:10.3390/ijms251810167
24. Machałowski T, Machałowska J, Gill K, Ziętek M, Piasecka M, Mrugacz G, et al. Sperm DNA Fragmentation Impairs Early Embryo Development but Is Not Predictive of Pregnancy Outcomes: Insights from 870 ICSI Cycles. Int J Mol Sci. 2025 Aug;26:7923. doi:10.3390/ijms26167923
25. Cano-Extremera M, Hervás I, Iranzo G, Guillem F, Juliá G, Navarro-Gomezlechon A, et al. Superior Live Birth Rates, Reducing Sperm DNA Fragmentation (SDF), and Lowering Miscarriage Rates by Using Testicular Sperm Versus Ejaculates in Intracytoplasmic Sperm Injection (ICSI) Cycles from Couples with High SDF: A Systematic Review and Meta-Analysis. Biology (Basel). 2025 Aug;14:130. doi:10.3390/biology14020130
26. Black H. A Synopsis of the Associations of Oxidative Stress, ROS, and Antioxidants with Diabetes Mellitus. Antioxidants. 2022;11(10):2003. doi:10.3390/antiox11102003

27. Chen X, Xie N, Feng L, Huang Y, Wu Y, Zhu H, et al. Oxidative stress in diabetes mellitus and its complications: From pathophysiology to therapeutic strategies. Chin Med J (Engl). 2024;138:15–27. doi:10.1097/cm9.0000000000003230
28. González P, Lozano P, Ros G, Solano F. Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections. Int J Mol Sci. 2023;24(11):9352. doi:10.3390/ijms24119352
29. Giri B, Dey S, Das T, Sarkar M, Banerjee J, Dash S. Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity. Biomed Pharmacother. 2018;107:306–28. doi:10.1016/j.biopha.2018.07.157
30. Khalid M, Petroianu G, Adem A. Advanced Glycation End Products and Diabetes Mellitus: Mechanisms and Perspectives. Biomolecules. 2022;12(4):542. doi:10.3390/biom12040542
31. Tang Z, Zheng Y. Prepubertal Diabetes Stagnates Testicular Development by Skewing Autophagy Homeostasis in Leydig Cells. Cells. 2025;14(17):1376. doi:10.3390/cells14171376
32. Tian Y, Song W, Xu D, Chen X, Li X, Zhao Y. Autophagy Induced by ROS Aggravates Testis Oxidative Damage in Diabetes via Breaking the Feedforward Loop Linking p62 and Nrf2. Oxid Med Cell Longev. 2020;2020:1–9. doi:10.1155/2020/7156579
33. Badejogbin O, Chijioke-Agu O, Olubiyi M, Agunloye M. Pathogenesis of testicular dysfunction in diabetes: exploring the mechanism and therapeutic interventions. J Assist Reprod Genet. 2024;42:367–79. doi:10.1007/s10815-024-03314-3
34. Shrilatha B, Muralidhara. Early oxidative stress in testis and epididymal sperm in streptozotocin-induced diabetic mice: its progression and genotoxic consequences. Reproductive toxicology. 2007;23 4:578–87. doi:10.1016/j.reprotox.2007.02.001
35. Venditti M, Romano M, Boccella S, Haddadi A, Biasi A, Maione S, et al. Type 1 diabetes impairs the activity of rat testicular somatic and germ cells through NRF2/NLRP3 pathway-mediated oxidative stress. Front Endocrinol (Lausanne). 2024;15(5). doi:10.3389/fendo.2024.1399256
36. Mohammadi N, Hemmati M, Motlagh B, Biyabani A. Betaine postpones hyperglycemia-related senescence in ovarian and testicular cells: Involvement of RAGE and β-galactosidase. Cell Biochem Funct. 2024;42(2):3973. doi:10.1002/cbf.3973
37. Wang Y, Fu X, Li H. Mechanisms of oxidative stress-induced sperm dysfunction. Front Endocrinol (Lausanne). 2025;16. doi:10.3389/fendo.2025.1520835
38. Biasi A, Ambruosi MR, Romano M, Boccella S, Falvo S, Guida F, et al. Impact of Type 1 Diabetes on Testicular Microtubule Dynamics, Sperm Physiology, and Male Reproductive Health in Rat. Int J Mol Sci. 2025;26(10):4579. doi:10.3390/ijms26104579
39. Soetan O, Ajao F, Ajayi A. Erythritol attenuates testicular dysfunction in diabetic rat via suppression of oxidative stress, inflammation and apoptosis. Biochem Biophys Res Commun. 2023;690:149254. doi:10.1016/j.bbrc.2023.149254
40. Yan LJ. Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. Animal Model Exp Med. 2018;1:7–13. doi:10.1002/ame2.12001
41. Tang W, Martin K, Hwa J. Aldose Reductase, Oxidative Stress, and Diabetic Mellitus. Front Pharmacol. 2012 May;3:87. doi:10.3389/fphar.2012.00087
42. Garg S, Gupta J. Polyol Pathway and Redox Balance in Diabetes. Pharmacol Res. 2022;106326. doi:10.1016/j.phrs.2022.106326
43. Szałabska-Rąpała K, Zych M, Borymska W, Londzin P, Dudek S, Kaczmarczyk-Żebrowska I. Beneficial effect of honokiol and magnolol on polyol pathway and oxidative stress parameters in the testes of diabetic rats. Biomed Pharmacother. 2024;172:116265. doi:10.1016/j.biopha.2024.116265
44. Erukainure O, Olasehinde T, Olayeriju O, Omotoso B, Islam MS, Olaniran A. Sulfated Polysaccharides From Gracilaria gracilis (Red Seaweed) Restores Testicular Glucose Metabolism by Improving FSH and Insulin

Signaling in Rats With Type 2 Diabetes. Mol Nutr Food Res. 2025 Dec 5;69(23):70280. doi:10.1002/mnfr.70280

45. Lei X, Huo P, Wang Y, Xie Y, Shi Q, Tu H, et al. Lycium barbarum Polysaccharides Improve Testicular Spermatogenic Function in Streptozotocin-Induced Diabetic Rats. Front Endocrinol (Lausanne). 2020;11. doi:10.3389/fendo.2020.00164
46. Twarda-Clapa A, Olczak A, Białkowska A, Koziołkiewicz M. Advanced Glycation End-Products (AGEs): Formation, Chemistry, Classification, Receptors, and Diseases Related to AGEs. Cells. 2022 Apr 12;11(8):1312. doi:10.3390/cells11081312
47. Darmishonnejad Z, Zadeh VH, Tavalaee M, Kobarfard F, Hassani M, Gharagozloo P, et al. Effect of Advanced Glycation end Products (AGEs) on Sperm Parameters and Function in C57Bl/6 Mice. Reproductive Sciences. 2024;31:2114–22. doi:10.1007/s43032-024-01507-w
48. Kim HJ, Jeong M, Jang S. Molecular Characteristics of RAGE and Advances in Small-Molecule Inhibitors. Int J Mol Sci. 2021 Jun 27;22(13):6904. doi:10.3390/ijms22136904
49. Wautier M, Guillausseau P, Wautier J. Activation of the receptor for advanced glycation end products and consequences on health. Diabetes Metab Syndr. 2017;11 4:305–9. doi:10.1016/j.dsx.2016.09.009
50. Omolaoye T, Du Plessis S. The effect of streptozotocin induced diabetes on sperm function: a closer look at AGEs, RAGEs, MAPKs and activation of the apoptotic pathway. Toxicol Res. 2020;37:35–46. doi:10.1007/s43188-020-00040-7
51. Mallidis RerNat, Agbaje I, McClure N, Kliesch S. Einfluss des Diabetes mellitus auf die Fertilität des Mannes. Urologe. 2011;50:33–7. doi:10.1007/s00120-010-2440-3
52. Chen Y, Jiao N, Jiang M, Liu L, Zhu Y, Wu H, et al. Loganin alleviates testicular damage and germ cell apoptosis induced by AGEs upon diabetes mellitus by suppressing the RAGE/p38MAPK/NF-κB pathway. J Cell Mol Med. 2020;24:6083–95. doi:10.1111/jcmm.15198
53. Browning J, Ghanim M, Jagoe W, Cullinane J, Glover L, Wingfield M, et al. Membrane-bound receptor for advanced glycation end products (RAGE) is a stable biomarker of low-quality sperm. Hum Reprod Open. 2024 Jan 1;2024(4):hoae064. doi:10.1093/hropen/hoae064
54. Mallidis C, Agbaje I, Rogers D, Glenn J, McCullough S, Atkinson A, et al. Distribution of the receptor for advanced glycation end products in the human male reproductive tract: prevalence in men with diabetes mellitus. Human reproduction. 2007;22 8:2169–77. doi:10.1093/humrep/dem156
55. Papadopoulou A, Karkalousos P, Trapali M. Effects of Diabetes Mellitus upon Sperm Quality Insight into Molecular Level. J Diabetes Mellitus. 2022;12(2):75–86. doi:10.4236/jdm.2022.122008
56. Karimi J, Goodarzi MT, Tavilani H, Khodadadi I, Amiri I. Increased receptor for advanced glycation end products in spermatozoa of diabetic men and its association with sperm nuclear DNA fragmentation. Andrologia. 2012 May;44:280–6. doi:10.1111/j.1439-0272.2011.01178.x
57. Mori Y, Terasaki M, Osaka N, Fujikawa T, Yashima H, Saito T, et al. DNA Aptamer Raised against Advanced Glycation End Products Improves Sperm Concentration, Motility, and Viability by Suppressing Receptors for Advanced Glycation End Product-Induced Oxidative Stress and Inflammation in the Testes of Diabetic Mice. Int J Mol Sci. 2024 May 29;25(11):5947. doi:10.3390/ijms25115947
58. Jiao N, Chen Y, Zhu Y, Wang W, Liu M, Ding W, et al. Protective effects of catalpol on diabetes mellitus-induced male reproductive damage via suppression of the AGEs/RAGE/Nox4 signaling pathway. Life Sci. 2020;116736. doi:10.1016/j.lfs.2019.116736
59. Gori P, Raval M, Patel S, Patel A, Solanki N, Patel P, et al. Argyreia nervosa (Brum.f.) Bojer. alleviates diabetes mellitus-induced male infertility. Mol Biol Rep. 2025 Dec 4;52(1):546. doi:10.1007/s11033-025-10654-5
60. Wright C, Milne S, Leeson H. Sperm DNA damage caused by oxidative stress: modifiable

clinical, lifestyle and nutritional factors in male infertility. Reprod Biomed Online. 2014 Jun;28(6):684–703. doi:10.1016/j.rbmo.2014.02.004

61. Sakkas D, Alvarez J. Sperm DNA fragmentation: mechanisms of origin, impact on reproductive outcome, and analysis. Fertil Steril. 2010;93 4:1027–36. doi:10.1016/j.fertnstert.2009.10.046
62. Conti D, Calamai C, Muratori M. Sperm DNA Fragmentation in Male Infertility: Tests, Mechanisms, Meaning and Sperm Population to Be Tested. J Clin Med. 2024 Sep 7;13(17):5309. doi:10.3390/jcm13175309
63. Qiu Y, Yang H, Li C, Xu CL. Progress in Research on Sperm DNA Fragmentation. Med Sci Monit. 2020 Apr;26:e918746. doi:10.12659/msm.918746
64. Dagar S, Verma S. Sperm DNA Fragmentation and Male Infertility: A Comprehensive Review. International Journal of Innovations in Science Engineering And Management. 2025 Jun 30;424–31. doi:10.69968/ijisem.2025v4i2424-431
65. Zurera-Egea C, Mateo S, Novo S, Asensio M, Boada M, Antich M, et al. The Utility of Sperm DNA Fragmentation as a Diagnostic Tool for Male Infertility and Its Predictive Value for Assisted Reproductive Technology Outcomes. Int J Mol Sci. 2025 Jun 30;26(13):6314. doi:10.3390/ijms26136314
66. Alahmar A, Singh R, Palani A. Sperm DNA Fragmentation in Reproductive Medicine: A Review. J Hum Reprod Sci. 2022;15:206–18. doi:10.4103/jhrs.jhrs_82_22
67. Ziouziou I, Rambhatla A, Shah R, Agarwal A. Sperm DNA fragmentation and infertility: a narrative review. World J Urol. 2024;42:1–8. doi:10.1007/s00345-024-05090-2
68. Nielsen J, Majzoub A, Esteves S, Humaidan P. Unraveling the Impact of Sperm DNA Fragmentation on Reproductive Outcomes. Semin Reprod Med. 2023;41:241–57. doi:10.1055/s-0043-1777324
69. Cissen M, Van Wely M, Scholten I, Mansell S, De Bruin J, Mol B, et al. Measuring Sperm DNA Fragmentation and Clinical Outcomes of Medically Assisted Reproduction: A Systematic Review and Meta-Analysis. PLoS One. 2016 Nov 10;11(11):e0165125. doi:10.1371/journal.pone.0165125
70. Esteves S, Santi D, Simoni M. An update on clinical and surgical interventions to reduce sperm DNA fragmentation in infertile men. Andrology. 2020;8:53–81. doi:10.1111/andr.12724
71. Andrabi S, Ara A, Saharan A, Jaffar M, Gugnani N, Esteves S. Sperm DNA Fragmentation: causes, evaluation and management in male infertility. JBRA Assist Reprod. 2024;28:306–19. doi:10.5935/1518-0557.20230076
72. Agarwal A, Majzoub A, Baskaran S, Selvam M, Cho C, Henkel R, et al. Sperm DNA Fragmentation: A New Guideline for Clinicians. World J Mens Health. 2020;38:412–71. doi:10.5534/wjmh.200128
73. Çayan S, Farkouh A, Agarwal A, Atmoko W, Wyns C, Arafa M, et al. Global Andrology Forum Clinical Guidelines on the Relevance of Sperm DNA Fragmentation in Reproductive Medicine. World J Mens Health. 2025;44:78–89. doi:10.5534/wjmh.250005
74. Llácer J, Requena A, Checa M, Bellver J, Bosch E, Espinós J, et al. The role of sperm DNA fragmentation in reproduction: a SWOT analysis. J Assist Reprod Genet. 2025;42:3633–53. doi:10.1007/s10815-025-03645-9
75. Su L, Wolfs D, Hivert M, Patel J, Richardson L, Charmant C, et al. 1135-P: Type 2 Diabetes Modulates DNA Methylation in Human Sperm. Diabetes. 2021 Jun 1;70(Supplement_1). doi:10.2337/db21-1135-p
76. Su L, Dreyfuss J, Bannitz RF, Wolfs D, Hansbury G, Richardson L, et al. Type 2 diabetes impacts DNA methylation in human sperm. Clin Epigenetics. 2025 Mar 20;17(1):49. doi:10.1186/s13148-025-01853-9
77. Chen X, Lin Q, Wen J, Lin W, Liang JX, Huang H, et al. Whole genome bisulfite sequencing of human spermatozoa reveals differentially methylated patterns from type 2 diabetic patients. J Diabetes Investig. 2019;11:856–64. doi:10.1111/jdi.13201
78. Ferraz-Bannitz R, Ozturk B, Efthymiou V, Wang H, Cruz A, Cummings C, et al. 1528-P: Sperm DNA Methylation Is Altered in Men

with Type 1 Diabetes. Diabetes. 2025 Jun 20;74(Supplement_1). doi:10.2337/db25-1528-p

79. Jazayeri M, Eftekhari-Yazdi P, Gilani MS, Sharafi M, Shahverdi A. Epigenetic modifications at DMRs of imprinting genes in sperm of type 2 diabetic men. Zygote. 2022;1–10. doi:10.1017/s0967199422000107
80. Rotondo J, Lanzillotti C, Mazziotta C, Tognon M, Martini F. Epigenetics of Male Infertility: The Role of DNA Methylation. Front Cell Dev Biol. 2021;Volume 9-2021. doi:10.3389/fcell.2021.689624
81. Minas A, Camargo M, Alves M, Bertolla R. Effects of diabetes-induced hyperglycemia on epigenetic modifications and DNA packaging and methylation during spermatogenesis; A narrative review. Iran J Basic Med Sci. 2024;27:3–11. doi:10.22038/ijbms.2023.69604.15173
82. Kaltsas A, Markou E, Kyrgiafini MA, Zikopoulos A, Symeonidis E, Dimitriadis F, et al. Oxidative-Stress-Mediated Epigenetic Dysregulation in Spermatogenesis: Implications for Male Infertility and Offspring Health. Genes (Basel). 2025 Jan 17;16(1):93. doi:10.3390/genes16010093
83. Pavlínková G, Margaryan H, Žatecká E, Valaskova E, Elzeinová F, Kubátová A, et al. Transgenerational inheritance of susceptibility to diabetes-induced male subfertility. Sci Rep. 2017 Jul 10;7(1):4940. doi:10.1038/s41598-017-05286-0
84. Ding G, Liu Y, Liu ME, Pan JX, Guo M, Sheng J, et al. The effects of diabetes on male fertility and epigenetic regulation during spermatogenesis. Asian J Androl. 2015;17:948–53. doi:10.4103/1008-682x.150844
85. Žatecká E, Bohuslavova R, Valaskova E, Margaryan H, Elzeinová F, Kubátová A, et al. The Transgenerational Transmission of the Paternal Type 2 Diabetes-Induced Subfertility Phenotype. Front Endocrinol (Lausanne). 2021;Volume 12-2021. doi:10.3389/fendo.2021.763863
86. Moazamian A, Saez F, Drevet J, Aitken R, Gharagozloo P. Redox-Driven Epigenetic Modifications in Sperm: Unraveling Paternal Influences on Embryo Development and Transgenerational Health. Antioxidants. 2025 May 9;14(5):570. doi:10.3390/antiox14050570
87. Nna V, Nna V, Bakar ABA, Ahmad AH, Mohamed M. Down-regulation of steroidogenesis-related genes and its accompanying fertility decline in streptozotocin-induced diabetic male rats: ameliorative effect of metformin. Andrology. 2019 Jan 4;7(1):110–23. doi:10.1111/andr.12567
88. Service C, Puri D, Azzawi S Al, Hsieh TC, Patel D. The Impact of Obesity and Metabolic Health on Male Fertility: A Systematic Review. Fertil Steril. 2023 Dec 1;120(6):1098–111. doi:10.1016/j.fertnstert.2023.10.017
89. Luo Z, Wang L, Luo J, Shi L, Wang L, Xie G. Antidiabetic agents and male fertility: unraveling the impact of glucose-lowering therapies on sperm quality in diabetic males—a narrative review. Transl Androl Urol. 2025;14:3387–401. doi:10.21037/tau-2025-440
90. Nguyen ND, Le MT, Tran NQT, Nguyen QHV, Cao TN. Micronutrient supplements as antioxidants in improving sperm quality and reducing DNA fragmentation. Basic Clin Androl. 2023 Sep 14;33(1):23. doi:10.1186/s12610-023-00197-9
91. Szabó A, Váncsa S, Hegyi P, Kói T, Ács J, Hermánné RJ, et al. Assessing the efficacy of varicocelectomy, antioxidants, FSH treatment, and lifestyle modifications on sperm DNA fragmentation: a systematic review and meta-analysis. Sci Rep. 2025 Mar 24;15(1):10118. doi:10.1038/s41598-025-93267-z
92. Tiwari P, Yadav A, Kumari D, Mishra R, Dada R. Sperm DNA fragmentation and yoga: A narrative review on enhancing male reproductive health. Pathol Res Pract. 2025 Dec;276:156269. doi:10.1016/j.prp.2025.156269
93. Martinez M, Majzoub A. Best laboratory practices and therapeutic interventions to reduce sperm DNA damage. Andrologia. 2021 Mar 14;53(2). doi:10.1111/and.13736
94. Romano M, Cirillo F, Spadaro D, Busnelli A, Castellano S, Albani E, et al. High sperm DNA fragmentation: do we have robust evidence to support antioxidants and testicular sperm

extraction to improve fertility outcomes? a narrative review. Front Endocrinol (Lausanne). 2023 Oct 5;14. doi:10.3389/fendo.2023.1150951

95. Rama Raju GA, Jaya Prakash G, Murali Krishna K, Madan K, Siva Narayana T, Ravi Krishna CH. Noninsulin-dependent diabetes mellitus: effects on sperm morphological and functional characteristics, nuclear DNA integrity and outcome of assisted reproductive technique. Andrologia. 2012 May;44:490–8. doi:10.1111/j.1439-0272.2011.01213.x
96. Imani M, Talebi AR, Fesahat F, Rahiminia T, Seifati SM, Dehghanpour F. Sperm parameters, DNA integrity, and protamine expression in patients with type II diabetes mellitus. J Obstet Gynaecol (Lahore). 2021 Apr 3;41(3):439–46. doi:10.1080/01443615.2020.1744114
97. Belladelli F, Boeri L, Pozzi E, Fallara G, Corsini C, Candela L, et al. Triglycerides/Glucose Index Is Associated with Sperm Parameters and Sperm DNA Fragmentation in Primary Infertile Men: A Cross-Sectional Study. Metabolites. 2022 Feb 3;12(2):143. doi:10.3390/metabo12020143
98. Chen MC, Lin JA, Lin HT, Chen SY, Yen G. Potential effect of advanced glycation end products (AGEs) on spermatogenesis and sperm quality in rodents. Food Funct. 2019;10 6:3324–33. doi:10.1039/c9fo00240e
99. Omolaoye T, Du Plessis S. Male Infertility: A Proximate Look at the Advanced Glycation End Products. Reproductive toxicology. 2020;93:169–77. doi:10.1016/j.reprotox.2020.02.002
100. He Z, Ge F, Li C, Zang M, Cao C, Zhang J, et al. The Remodeling of Mitochondrial-Endoplasmic Reticulum Contacts by Omega-3 Fatty Acids Mitigates Dietary Advanced Glycation End Product-Driven Sertoli Cell Senescence and Oligoasthenozoospermia. Int J Biol Sci. 2025;21:6042–61. doi:10.7150/ijbs.117091
101. Ribas-Maynou J, García-Peiró A, Fernández-Encinas A, Abad C, Amengual M, Prada E, et al. Comprehensive analysis of sperm DNA fragmentation by five different assays: TUNEL assay, SCSA, SCD test and alkaline and neutral Comet assay. Andrology. 2013 Sep;1(5):715–22. doi:10.1111/j.2047-2927.2013.00111.x