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The impact of diabetes on spermatogenesis

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Abstract

Diabetes mellitus, a chronic metabolic disease characterized by persistent hyperglycemia, has been shown to have a significant impact on several body systems, including the male reproductive system, spermatogenesis, the process of sperm formation and development in the testes, can be adversely affected by the direct and indirect effects of diabetes, the main mechanisms involving oxidative damage, hormonal alterations, mitochondrial dysfunction and endoplasmic stress, The main mechanisms involve oxidative damage, hormonal alterations, mitochondrial dysfunction and endoplasmic stress, which can lead to a reduction in the quality and quantity of spermatozoa, as well as in their motility and morphology. In addition, diabetes can induce chronic inflammation and affect the integrity of the blood-testicular barrier, which alters the microenvironment necessary for healthy spermatogenesis, in the present communication we describe the theoretical aspects of the effects of diabetes on seminal fluid with emphasis on spermatogenesis as well as its impact on male fertility.

Keywords: Diabetes mellitus; Spermatogenesis; Male fertility; Alterations to DNA

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies, characterized by chronic hyperglycemia and disturbances in the metabolism of carbohydrates, fats, and proteins resulting from defects in insulin secretion, insulin action, or both [1]. Globally, it is estimated that 382 million people suffer from diabetes, with a prevalence of 8.3% [2]. The number of cases has increased dramatically, rising from 108 million in 1980 to 422 million today, with diabetes being more common in low- and middle-income countries than in high-income countries [3].

The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs. One of the most relevant complications is the impairment of the male reproductive system [4]. Both type 1 and type 2 diabetes, whether naturally occurring or experimentally induced, can negatively affect male fertility. These effects include reduced sperm motility, DNA damage in sperm cells, and alterations in the components of seminal plasma [5].

In healthy men, the estimated time required to produce ejaculated sperm ranges from 42 to 76 days, with a daily sperm production of 150 to 275 million However, diabetes can significantly disrupt this process, compromising the quality and functionality of sperm cells [6].

In this article, we will analyze the process of spermatogenesis, which is essential for the production and maturation of sperm cells, as well as the impact that certain chronic diseases, such as diabetes, can have on this mechanism. We will focus on how these conditions can alter fertility-related genes and how these alterations provide insight into other ways chronic diseases affect the body.

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Some diseases do not directly impact fertility genes but cause damage in specific regions of DNA that may be linked to the activation of genes associated with metabolic disorders. An important example is obesity, where genetic damage in sperm cells is often associated with more complex metabolic dysfunctions. This phenomenon will be examined at the end of the article to provide a comprehensive perspective on how chronic diseases influence both reproduction and other biological systems.

2. Influence of diabetes mellitus on structural changes in the testis.

Diabetes mellitus can induce significant structural changes in the testes, affecting male reproductive function. Studies in animal models have provided valuable information on these changes [7].

In alloxan-induced diabetic rats, a decrease in testicular mass and progressive atrophy of the germinal epithelium in the seminiferous tubules have been observed. This includes cytoplasmic vacuolization, detachment of germ cells into the tubular lumen and the appearance of giant cells. Leydig cells are abnormally distributed, and hyperplasia of Sertoli cells is observed. In addition, ultrastructural changes involving the cytoplasm, organelles, and cell nuclei of germ, Sertoli, and Leydig cells have been documented, with accumulation of lipid droplets and dense dark material in the cytoplasm, cell degeneration, and apoptosis [7].

In streptozotocin-induced diabetic rats, a decrease in seminiferous tubule diameter and spermatogenic activity has been reported, with a reduction in plasma testosterone levels [8]. Diabetes is also associated with increased oxidative stress, which affects Leydig cell function and may contribute to decreased testosterone and alterations in the seminiferous epithelium [9].

In mice with type 2 diabetes, a decrease in testosterone levels and testicular weight, as well as a reduction in seminiferous tubule cross-sectional area and cell layer thickness have been found. A decrease in the number of Sertoli and Leydig cells has also been observed. Diabetes has been associated with increased expression of collagen IV and laminin α5 in seminiferous tubules, which may contribute to spermatogenic dysfunction [10].

3. Oxidative stress from diabetes causes sperm damage

DNA damage in diabetic vasculature is an important stimulus for the initiation of mechanisms that result in endothelial dysfunction and finally vasculopathy. It is also quite possible that the metabolic products generated due to supraphysiological levels of glucose in diabetes can lead to an abnormal environment and generate oxidative stress [11].

Oxidative stress caused by an imbalance between free radicals and antioxidants has detrimental effects on sperm DNA. Damage to sperm DNA, particularly mitochondrial DNA, is one of the main consequences of oxidative stress in diabetics. Damage to mitochondria affects sperm motility, as mitochondria are essential for generating the energy needed for motility. In addition, sperm DNA fragmentation is significantly higher in men with diabetes, which is related to an increased risk of sperm motility.

Diabetes, which is related to an increased risk of male infertility due to lower semen quality [12].

Among the pathologies where damage caused by oxidative stress has been studied is male infertility. Spermatozoa require small amounts of ROS (reactive oxygen species) to begin capacitation, as well as the acrosomal reaction and fusion with the oocyte membrane during fertilization; however, when this environment is altered, changes occur in their ability to fertilize [13].

Spermatozoa are particularly susceptible to oxidative stress-induced damage due to the high volume of polyunsaturated fatty acids in their membranes. As a consequence of this imbalance, the lipoperoxides generated inhibit the fertilizing capacity of spermatozoa. Studies suggest that between 30% and 80% of infertile men have oxidative stress [14].

4. Semen quality in diabetic patients

Diabetes can impair the development, maturation and functional capacity of sperm. In addition, the sperm of men with diabetes age prematurely, which reduces the chances of achieving a pregnancy with these gametes.

Because of all these factors, men with diabetes may experience a reduction in the quality of their semen, including a decrease in sperm motility, volume and concentration, as well as increased DNA damage. All of these can lead to male infertility, as semen quality is essential for successful fertilization and embryo development [15].

Motility is impaired due to damage to sperm mitochondria, which are essential for providing energy. In addition, advanced glycation end products (AGEs) and diabetes-induced oxidative stress damage the structural integrity of spermatozoa [16]. Studies indicate that although diabetic men show sperm concentration, motility and morphology within normal parameters by conventional standards, they have higher levels of nuclear DNA fragmentation (nDNA) and mitochondrial DNA deletions (mtDNA). The nDNA fragmentation is significantly higher in diabetic men (53%) compared to the control group (32%), suggesting that diabetes is associated with sperm DNA damage that could affect fertility [17].

This genetic damage may be the result of oxidative stress, an imbalance between free radicals and antioxidants in the body. In addition, men with diabetes have higher levels of advanced glycation end products (AGEs), which have been shown to induce oxidative stress and damage sperm DNA. AGEs are compounds formed by the binding of proteins and sugars, and are found in higher amounts in the reproductive tracts of diabetic men, which could further contribute to sperm DNA damage [18].

5. Glucose metabolism in spermatogenesis

Hyperglycemia induced spermatogenesis arrest has been demonstrated in various studies. Moreover, various sperm maturation processes related to sperm function such as motility are directly depending on glucose metabolism in Sertoli cells. It has been demonstrated that diabetes-induced hyperglycemia adversely impacts sperm morphology, motility and DNA integrity, leading to infertility. However, fertility quality is another important factor to be considered. Diabetes-induced hyperglycemia is not only impacting sperm functions, but also affecting sperm epigenome. DNA packing process and epigenetics modifications occur during spermatogenesis process, determining next generation genetic quality transmitted through sperm. Critical damages may occur due to under or downregulation of key proteins during spermatogenesis. Consequently, unpacked DNA is more exposed to oxidative stress, leading to intensive DNA damages. Moreover, epigenetic dysregulation occurred during spermatogenesis may impact embryo quality and be transmitted to next generations, increasing offspring genetic issues [19].

A study demonstrated that loss of glucose control results in decreased sperm motility only without alterations in any other parameter of sperm quality [20]. Another study showed that sperm chromatin damage is increased in T1D-induced hyperglycemia [21]. Finally, a semen proteomic study demonstrated altered proteomic profile in hyperglycemic T1D men compared to normoglycemic individuals. Results indicated the accumulation of modified forms of the eppin (epididymal proteinase inhibitor) protein complex (EPC) components semenogelin-1, clusterin, and lactotransferrin in the sperm proteomes, all of which present important roles in fertilization [22].

It was found that mice on a high-fat diet (HFD) from 21 days after birth until adulthood (200 days) developed prediabetes, along with irreversible lipid damage and changes in testicular lipid content and metabolism. This led to a permanent reduction in sperm quality. But that's not all, these metabolic changes and reduced sperm quality don't just affect the mice on the diet. They're also heritable. These alterations impact the testicular metabolome and sperm quality in subsequent generations [23].

Sirt1 plays a key role in germ cell survival, glucose metabolism in testicular tissue, and mitochondria respiration. For instance, Sirt1 gene deletion results in disruption of spermatogenesis. AMPK in association with Sirt1 maintains and regulates mitochondrial biogenesis and in association with PGC-1 regulates oxidation of fatty acids, ATP synthesis, and lipid homeostasis [24,25]

6. Epigenetic edits to spermatogenesis and obesity genes

The most studied epigenetic marks are the addition of a methyl group to DNA. [26]. CpG islands are found in the promoter regions of approximately 40% of genes. The DNA methylation process is a consequence of the action of DNMT enzymes. The enzymes DNMT3a, DNMT3b and DNMT3L (DNA methyltranferase 3a, 3b and 3L, respectively) are responsible for methylation de novo in mammalian spermatozoa. The first two catalyze the methylation reaction, while DNMT3L facilitates the action of DNMT3a and DNMT3b and coordinates the correct positioning of the methylation marks [27].

The importance of methylation for individual fertility is demonstrated in studies performed in knockout mice for one of these genes. In these studies, disruption of the *DNMT3L* causes infertility in the individual carrier [28]. Furthermore, although fertilization can occur in the absence of proper establishment and maintenance of DNA methylation, the resulting embryo is unable to develop properly [29].

In another series of studies, also performed in a mouse model, the function of the histone demethylase enzyme JHMD2A, which plays an important role in both male infertility and obesity, was analyzed [30]. In particular, the authors of this study described how JHDM2A binds directly to the promoter regions of two genes vital for proper DNA packaging in the sperm nucleus: the *Tnp1* (nuclear transition protein) gene and the *Prm1* (protamine 1) gene. Binding of JHDM2A induces its transcriptional activation by demethylating residues in H3K9 [31]. If the packaging is not performed correctly, fertility is impaired. In addition, this enzyme also regulates the transcription of genes involved in lipid metabolism, so that *knockout* mice for this protein exhibit obesity and hyperlipidemia. Among the genes regulated by JHDM2A is PPARα [32].

7. Prediabetes alters methylome patterns in spermatozoa

Paternal prediabetes altered the overall methylome patterns in sperms with a large portion of differentially methylated genes overlapping with that of pancreatic islets in offspring, indicating that paternal prediabetes increased the susceptibility to diabetes in offspring through gametic epigenetic alterations. The study discovered that paternal prediabetes alters overall methylation patterns in sperm. They isolated sperm from control and prediabetic males and surveyed cytosine methylation patterns across the entire genome by MeDIP-Seq [33]. Notably, global cytosine methylation profiles were altered in prediabetes samples compared with controls, and the methylation of 263 upstream2k, 278 downstream2k, 121 5'UTR, 247 3'UTR, 1299 CDS, and 4354 intron element-associated genes were changed, respectively. They observed that a large proportion of differentially methylated genes identified in sperm overlapped with that of pancreatic islets. Specifically, they observed that certain genes (such as Pik3ca and Pik3r1) can partially resist global demethylation postfertilization and largely inherit cytosine methylation from sperm, further suggesting that there is intergenerational transmission of cytosine methylation at a substantial fraction of the genome [34].

8. Conclusion

Diabetes has a profound impact on spermatogenesis and male fertility, primarily through mechanisms such as oxidative DNA damage, mitochondrial dysfunction, and compromised chromatin compaction. These alterations, driven by chronic hyperglycemia, significantly affect the genetic integrity of sperm, reducing their ability to fertilize an egg and potentially influencing the quality of embryos and the long-term health of offspring. One of the most critical factors is the high levels of reactive oxygen species (ROS) in diabetic individuals, which interfere with DNA repair processes and disrupt the protective mechanisms necessary to maintain sperm genome integrity.

The influence of genetic predispositions further complicates the relationship between diabetes and male fertility. Variants in genes involved in oxidative stress regulation, mitochondrial function, and inflammation increase the susceptibility to testicular damage, amplifying the negative effects of diabetes on reproductive health. Additionally, mutations or polymorphisms in genes related to endocrine pathways can exacerbate the metabolic disturbances caused by diabetes, creating a complex interplay between genetic and environmental factors.

Given the multifaceted nature of diabetes-related reproductive damage, it is crucial to adopt a comprehensive approach to its management. Strategies should not only focus on achieving glycemic control but also aim to reduce oxidative stress, protect the testicular microenvironment, and mitigate genetic damage. Early interventions addressing these aspects are essential to preserving fertility and ensuring better reproductive outcomes in men with diabetes. This underscores the broader importance of understanding the intricate connections between metabolic and genetic factors in managing chronic diseases like diabetes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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