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Review

# Sperm glucose transport and metabolism in diabetic individuals

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ABSTRACT

Individuals with diabetes mellitus (DM) present marked reduction in sperm quality and higher DNA damage in spermatozoa, evidencing that this metabolic disorder impairs male fertility. These effects are related to defective testicular metabolic pathways and signaling, resulting in altered sperm metabolism. Spermatozoa metabolize several substrates to ensure energy supplies and any alteration in this feature compromise sperm quality. For ATP production, spermatozoa require substrate availability and the involvement of specific hexose membrane carriers. DM is known to modulate the spermatozoa substrate consumption and/or production due to altered glycolytic behavior. In fact, glucose uptake and metabolism is highly deregulated in diabetic individuals. Herein, we present an overview of the implications of DM in sperm glucose uptake and metabolism. The understanding of these processes is essential to identify key mechanisms associated with DM-related male (in)fertility. Moreover, it may contribute to the development of therapeutics to counteract the dysfunction induced by DM in sperm metabolism.


**Contents**



## 1. Introduction

Diabetes mellitus (DM) is a metabolic disorder that has become one of the most serious problems of modern societies due to its long-term health complications (Coman et al., 2012). Several studies have linked DM to male reproductive alterations (Ballester et al., 2004), revealing that diabetic males present a marked reduction in fecundity (Ballester et al., 2004; Cameron et al., 1990; Frenkel et al., 1978; Murray et al., 1983; Scarano et al., 2006), impairment of sperm quality (Amaral et al., 2006; Scarano et al., 2006) and higher percentage of spermatozoa with nuclear DNA damage (Agbaje et al., 2007). The complications induced by DM in the testicular function have been related to the lack of insulin (Ballester et al., 2004), which is the leading hormone responsible for glucose homeostasis (Bogan, 2012). Glucose homeostasis is crucial for the maintenance of spermatogenesis *in vivo* and for the preservation of the fertility capacity of the male sperm (D'Cruz et al., 2012a, 2012b; Mancine et al., 1960; Zysk et al., 1975). As DM is increasingly affecting more men during reproductive years, it is expected that the male fertility problems associated with DM will dramatically rise in the near future. Hence, there is a growing interest in preventing DM and/or reducing its associated reproductive comorbidities. It is important to elucidate the molecular mechanisms associated with the development of these comorbidities in order to find new therapies to counteract the severe consequences of DM.

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## 2. Diabetes mellitus: an overview

DM is a treatable but incurable lifelong disease characterized by a hyperglycemic state. Individuals suffering from this condition present defects in protein, fat and carbohydrate metabolism, mostly due to a malfunctioning in insulin secretion and/or insulin resistance (American Diabetes Association, 2013; Ugochukwu et al., 2003), defects in reactive oxygen species (ROS) production and scavenging defenses (Kesavulu et al., 2000), and high oxidative stress (OS) (Baliga and Sapsford, 2009; Hamden et al., 2011). The number of diabetic individuals has been rapidly increasing worldwide. According to recent statistics, by the year 2030, the number of diabetic patients is expected to reach an alarming number of 366 million (Wild et al., 2004). The increasing prevalence of obesity, along with the lack of physical activity, the growth of global population, the aging and the urbanization are strong contributors to the epidemic proportions of DM (Wild et al., 2004). Several specific characteristics allow the classification of DM into two different types, commonly called type 1 and type 2. Type 1, or insulin-dependent DM (T1DM), is usually caused by an autoimmune reaction in which the body's defense system attacks insulin-producing pancreatic beta cells in genetically susceptible individuals (Burul-Bozkurt et al., 2010; Grieco et al., 2012). T1DM develops more often in children and young adults, but it may affect people of any age (Agbaje et al., 2007). Individuals with this type of DM produce very little or no insulin, so, in order to survive, they need to control their blood glucose levels with exogenous insulin. The pathogenic factors that lead to T1DM are not fully elucidated yet. However, there is clear evidence that it develops due to alterations in the immune regulation (Heltianu et al., 2011). On the other hand, type 2 DM (T2DM) is characterized by insulin resistance (IR) and is responsible for the great majority (90–95%) of all DM cases (American Diabetes Association, 2013). IR is described as the inability of cells to respond to normal circulating levels of insulin (Berg et al., 2002), leading to the development of T2DM. This is a progressive process because of the limited capacity of pancreatic cells to augment the secretion of insulin to counterbalance IR, maintaining glucose tolerance at normal levels. However, eventually, this compensation is committed and impaired glucose tolerance (IGT) develops (DeFronzo et al., 1992), originating the so-called prediabetes, an intermediate state between normal glucose tolerance and evident T2DM (Edelstein et al., 1997). The awareness of prediabetes could strongly prevent the progression to DM (Aroda and Ratner, 2008; Hamman, 2009). Despite genetic predisposition, the risk of developing T2DM in humans increases with age, obesity, cardiovascular diseases and lack of physical activity (Carneiro et al., 2010; Golay and Ybarra, 2005). Usually, these individuals do not need exogenous treatment with insulin to survive and for that reason T2DM is commonly known as non-insulin-dependent DM (American Diabetes Association, 2013).

DM chronic hyperglycemia contributes to the onset of many systemic complications such as cardiovascular diseases and hypertension. It can also bring about long-term damage or dysfunction of diverse organs (eyes, kidneys, nerves, heart and blood vessels) as well as sexual dysfunction (American Diabetes Association, 2013). Thus, the need of preventing those comorbidities makes out of DM a vast field of research for researchers all over the world.

## 3. Male fertility and diabetes

Since the 11th century researchers have been trying to clarify the bonds between DM and male fertility, describing DM as "a collapse of sexual functions". In the last few years, the deleterious effects of DM on male fertility have become a matter of continuous debate due to its rapidly increasing incidence and the fact that the first diagnosis is taking place in increasingly younger individuals (Harjutsalo et al., 2008; Lavizzo-Mourey, 2007). So, the notion that DM is usually an elderly's disease has been quickly disregarded. Nowadays, DM is affecting more and more individuals prior to and during their reproductive years (Delfino et al., 2007; Nguyen et al., 2007), which supports the importance of studying DM-associated effects in male sexual function (Agbaje et al., 2007).

The hormonal and metabolic changes associated with DM (Bener et al., 2009; Mallidis et al., 2009) as well as obesity (Pauli et al., 2008) and metabolic syndrome (Kasturi et al., 2008) are key contributors to the development of male infertility. Clinically, infertility is defined as the inability to conceive after 1 year of unprotected intercourse (Zegers-Hochschild et al., 2009) and it affects about 13–18% of the couples worldwide (Dube et al., 2008). Interestingly, the male factor is the exclusive origin in about one third of the cases (Shukla et al., 2012). However, in a large number of these cases the cause for male infertility is unknown (de Kretser, 1997; Dohle et al., 2005; Seshagiri, 2001). In general, subfertility describes any form of reduced fertility in couples unsuccessfully trying to conceive (Jenkins et al., 2004). It has been reported that 50% of all diabetic male individuals have some grade of subfertility and/or infertility (La Vignera et al., 2009). One of the major problems contributing to subfertility and/or infertility in male diabetic individuals is the defective sperm quality due to abnormal sperm parameters such as motility, morphology, concentration and DNA fragmentation (du Plessis et al., 2011; Iammarrone et al., 2003). Several studies using animal models have shown that DM leads to a marked reduction in fecundity (Ballester et al., 2004; Cameron et al., 1990; Frenkel et al., 1978; Murray et al., 1983; Scarano et al., 2006) by decreasing sperm concentration and motility, increasing seminal plasma abnormalities and altering the normal morphology of sperm cells (Amaral et al., 2008). DM leads to irreversible damages in sperm nuclear and mitochondrial DNA as one of its many outcomes is the augmented levels of OS (Kasturi et al., 2008; Kort et al., 2006). Other disturbances such as retrograde ejaculation, premature ejaculation, decreased libido, delayed sexual maturation and impotence are also known to occur in patients with DM (Kandeel et al., 2001; La Vignera et al., 2012).

Apparently, the effects induced by DM on testicular functioning are a consequence of the lack of insulin (Ballester et al., 2004), that leads to a severe disruption in the distinctive glucose metabolism of testicular cells. There are studies suggesting that spermatogenesis disruption and germ cell apoptosis in T1DM are related to local autoimmune damage (La Vignera et al., 2012). Hence, the exact role of insulin in the regulation of male reproductive function needs in-depth research. Regarding T2DM, the infertility prevalence has been reported to be approximately 35% (La Vignera et al., 2012). Men with T2DM usually present impaired sperm parameters and decreased testosterone serum levels (La Vignera et al., 2012). So, as male fertility problems appear to be more exacerbated in patients with DM, it is crucial to highlight the key regulatory mechanisms by which spermatogenesis and sperm maturation are affected by this disease.

## 4. Glucose uptake and metabolism in sperm cells

Spermatogenesis is a multi-step process of germ cell division and development that takes place within the testis, more specifically on the seminiferous tubules (Walker, 2010). This process is under strict hormonal control and depends upon the cooperation established between the various testicular cells (Alves et al., 2013a). While the resulting mature sperm cells present specific metabolic needs, using external hexoses, such as glucose, as their main substrate (Angulo et al., 1998; Miki, 2007; Scott et al., 1962; Setchell et al., 1967; Terner, 1960), developing germ cells rely on the metabolic cooperation established with the somatic Sertoli cells (SCs), which have the ability to produce lactate at high rates (Fig. 1) (Boussouar and Benahmed, 2004). This is a key feature of testicular