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Diabetes Mellitus and male reproductive function: where we stand?

Editorial

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Diabetes mellitus (DM) is a metabolic disorder caused by absolute (Type 1 diabetes) or relative (Type 2 diabe-tes) deficiency of insulin and is associated with altera-tions in carbohydrate, lipid and protein metabolism [1]. The disease has been closely related with a wide range of long-term systemic complications and co-morbidi-ties, such as renal failure or hypertension [2]. Thus, the study of DM implications in human health is a chal-lenge to experts of any field of research.

According to the latest factsheets from World Health Organization (WHO), DM is one of the most rapidly growing threats to public health in modern societies. Over the past twenty years, the global prevalence of DM has approximately increased six-fold and nearly 350 million people worldwide suffer with the disease. The WHO estimated that, in 2004, over 3 million peo-pledied from consequences of high blood sugar and estimates that DM-related deaths will increase by two thirds between 2008 and 2030[1,3]. Nonetheless, the existing statistical data can be underestimated since the factors known to be responsible for the disease progression, such as obesity and lifestyle habits, may ag-gravate these numbers [2].

When we take a close look at fertility rates in mod-ern societies, we observe that the increase incidence of DM is concurrent with the falling birth rates and decreased fertility [4,5]. This fact is partly due to the alarming upraising of the number of men developing DM during the reproductive age. Indeed, the great ma-jority of patients with type 1 diabetes (T1D) are diag-nosed before the age of 30 [6] and there is an worry-ing number of childhood and adolescent with type 2 diabetes (T2D)[7]. Moreover, western lifestyle habits, together with the increasing obesity among young in-dividuals strongly contribute for the high incidence of T2D in youth[2]. DM is responsible for several bio-chemical and homeostasis alterations that may result in male subfertility and or infertility yet the real impact of DM on male reproductive health remains undisclosed. Although there is some controversy on the subject, the diabetic individuals are frequently described to pos-sess some sexual neuropathies, such as reduction of sexual appetite [8], that are explained with lethargy and tiredness related with the hyperglycemic state. Other disorders such as erectile dysfunction(ED) [9] or ret-rograde ejaculation [10,11] are also well known to occur in male diabetics. Nonetheless, when examining sperm parameters and sperm quality markers, the lit-erature shows some conflicting results. There are sev-eral studies since the 70's comparing young or adult diabetics with control individuals. While some studies report that diabetic men present lower sperm counts and significant differences in sperm motility and mor-phology [12], as well as in sperm volume and count [13], other report only a slight, non-significant, de-crease in sperm counts, although sperm volume and motility are frequently lower [14]. Others reported that sperm count and concentration were increased in the ejaculated of diabetic individuals, although sperm mo-tility and semen volume were decreased. Noteworthy, in these last studies, sperm morphology and motility were described to remain unaffected [15]. Yet, other more recent study reported no correlations between sperm motility and age, age of onset of T1D and duration. The same study reported also that several sperm motility parameters such as track speed, path velocity, progressive velocity, and lateral head displacement re-mained unchanged while others, such as linearity and linear index (which reveal the straightness of sperm swimming), were increased in diabetic men [16]. This study evidenced that the T1D effects in male fertility may be related to the disease complications and not the disease itself [16]. Interestingly, the sperm of dia-betic individuals is reported to present high fructose and glucose content [14], but the relation between an ineffective metabolic control and the observed altera-tions in the semen was never established and there-fore should deserve a special focus in the next years. An extensive study of spermatozoa cryopreservation from patients with various pathologies, reported that only sperm from diabetic men presented significant differences in sperm parameters[17], while a recent study reported no alterations in semen parameters from T1D and T2D individuals [6]. Nonetheless, these authors reported that sperm from diabetic men pre-sented a higher level of damage in sperm nuclear and mitochondrial DNA [6]. Although most of the studies are focused on sperm parameters analysis, there is an important study from 1985, performed using testicular biopsies from impotent men with DM that reported ultrastructural lesions in Sertoli cells (SCs) cytoplasm and morphological changes in the interstitial compartment of diabetic men testes [18]. These anatomic, structural and morphological alterations suggested that diabetic men may suffer a disruption on the sper-matogenic event resulting in the subfertility and/or in-fertility often associated with DM.

Even though there are apparent contradictory results concerning sperm parameters and the real impact of DM in male reproductive function, it is not consensual that DM effects are only reflected in sperm or in the ejaculated. Moreover, apart from the direct studies of sperm, new important findings have been reported using in vitro strategies. For instance, diabetic individuals are known

to have fluctuations in sex hormones con-centrations [19]. Recent in vitro studies with rat [20] and human [21] SCs showed that sex hormones are able to modulate these cells metabolism. This is very significant since SCs metabolism is a crucial event for a successful spermatogenesis. These cells are known as "nurse cells" since one of their main functions is to metabolize glucose into lactate that is then consumed by the developing germ cells [22]. Thus, the hormonal control of SCs metabolism has a direct effect on sper-matogenesis [23] and should deserve special attention when studying metabolic diseases that are also related with hormonal (de)regulation. Moreover, diabetic in-dividuals have severe insulin deregulations that should be taken in consideration when discussing the effects of DM. Euglycemia is very difficult to maintain in dia-betic patients and hypoglycemia/hyperinsulinemia, as well as hyperinsulinemia/hypoglycemia, are common events that diabetic individuals may face daily. There-fore, insulin can have a major role in the male sexual dysfunction associated with DM. In fact, recent re-ports show that only a few hours of insulin depriva-tion can alter not only SCs glucose metabolism [24] and also completely suppresses in vitro acetate pro-duction [25]. The regulation performed by insulin in these crucial processes for a normal spermatogenesis is a clear evidence that the molecular mechanisms by which DM affects the male reproductive function may also be linked to insulin fluctuations and not only to glucose concentrations.

There is an urgent need for clarification if DM can alter sperm parameters and overall male reproductive function. Furthermore, there is also a lack of consen-sus concerning sperm analysis, and it has been recently discussed thatconventional sperm analysis is very limit-ed and needs standardization before it can give definite answers relatively to the fertility status of individuals [26]. Besides, when assessing the effect of DM, there are several factors very difficult to control such as the duration of the disease, the glycemic levels, type of treatment, as well as all the comorbidities associated , that may obscure the real impact of DM in male fertili-ty. It is evident that not all diabetic men are infertile and sperm analysis is not able to give an absolute answer to the question. Nonetheless, the molecular mechanisms of spermatogenesis and sperm maturation might be altered even when conventional sperm parameters ap-pear normal. Thus, it is imperative to focus not only in the mechanisms that have a direct effect in natural and assisted conception, such as DNA integrity and oxidative stress, but also in the molecular basis of the disease that may affect testicular cells, spermatogen-esis, sperm production and sperm maturation. These molecular studies may not only open new insights on the DM effects in the male reproductive function, but also point toward possible therapeutic sites for inter-vention to decrease DM-related male subfertility and/ or infertility.

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