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The Antidiabetic Drug Metformin and Male Reproductive Function: An Overview

Editorial

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Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin action, insulin secretion, or both [1]. These defects lead to disturbances in carbohydrates, lipid and protein metabolism causing systemic complications and co-morbidities, particularly in renal and cardiovascular systems [2]. This disease is reaching pandemic proportions and a recent report estimated that more than 300 million of people worldwide already have DM and, alarmingly, some projections suggest that the number of diabetic patients will reach nearly 600 million by the year 2035 [3].

In contrast with DM prevalence, the fertility rates have been declining in the recent decades. Interestingly, these two events appear to be related for various reasons [4]. One of these reasons is the alarming increase of the number of men developing DM during the reproductive age. The vast majority of type 1 DM cases are diagnosed before the age of 30 [5] and there is an increasing number of children and adolescents with type 2 DM (T2DM) [6]. Thus, due to its complexity and the dramatic increase of diabetic patients, it urges to study the implications of DM in human reproductive health, particularly on male fertility.

When prescribing a treatment for DM, a complex analysis is needed to find the most suitable antidiabetic drug [7]. Several of these compounds, if not all, have the ability to modulate cellular metabolism in a manner that may benefit some organs, but damage others. Metformin is a biguanide, considered the first-line treatment for T2DM [7]. It is an insulin-sensitizing drug that exerts its anti-hyperglycemic effects by increasing the skeletal muscle uptake of glucose and reducing the absorption of glucose in the intestinal mucosa [8, 9]. Moreover, it blocks liver gluconeogenesis through regulation of the gluconeogenic flux [9]. Nevertheless, although a common feature has already been attributed to this drug in promoting the activity of AMP-activated protein kinase (AMPK) [10], the exact molecular mechanisms of metformin action remain to be fully disclosed, despite several decades of research focused on this drug action [9].

While metformin is presently being used for the management of female reproductive function, namely for the treatment of polycystic ovary syndrome [8], its effects on human male reproductive function remain largely unknown. The vast majority of the data available was obtained in studies conducted on animal models, particularly rodents. Moreover, the existing results remain controversial with some conflicting data. While data derived from exposing healthy animals to metformin resulted in the observation of deleterious reproductive effects, data obtained from diabetic animal models reinforce the therapeutic potential of this drug in protecting male reproductive health against the deleterious effects of DM. In fact, healthy male animals exposed to metformin exhibited adverse reproductive outcomes that involved decreased testosterone production [11], reduced testes size and seminiferous tubules diameter, with reduction on Sertoli cell numbers and concomitant decrease in sperm quality parameters [12]. Contrastingly, in studies where diabetic animal were exposed to metformin, it has been consistently reported that this drug can improve the male reproductive function and the spermatogenic index [13, 14]. Indeed, metformin administration was able to restore testosterone, LH and FSH levels on the testes of streptozotocin-induced diabetic rats [13]. A protective role has also been ascribed for metformin on male reproductive function of diabetic animals, not only by improving steroidogenesis and the antioxidant status of the testes (usually linked to an overproduction of ROS due to the hyperglycemic environment), but also by leading to an amelioration of sperm concentration and motility and of the percentage of morphologically normal sperm [13-16]. Although the literature shows some contradictory results when examining the effect of DM on human and animal sperm parameters and sperm quality markers, most of the studies reported a positive influence of metformin on sperm parameters [17, 18]. In fact, men with metabolic syndrome treated with metformin presented a significantly amelioration on sperm concentration, motility and morphology, which was attributed to the increase of LH and testosterone lev-

els [18]. Furthermore, male diabetics present an increased risk of developing particular sexual disorders, such as erectile dysfunction or retrograde ejaculation [19]. The treatment with metformin was shown to increase the contractility in the corpora cavernosa, improving the erectile function observed in a hypertensive model. The exposure to this drug was also reported to increase endothelial nitric oxide synthase phosphorylation, an important factor in erectile function, which is normally decreased in patients with erectile dysfunction, namely male diabetic individuals [20].

In vitro studies also support the therapeutic potential of metformin in protecting male reproductive health. In a recent study, our team has reported a stimulation of lactate production in rat Sertoli cells exposed to metformin [8]. Lactate production by Sertoli cells is a crucial event since this metabolite is the preferred energy substrate for developing germ cells and has an important anti-apoptotic effect [21]. Thus, the increase in lactate production caused by metformin may be positive for spermatogenesis and male reproductive function. Several other studies provided evidence that metformin acts as an inhibitor of complex I of the mitochondrial electron transport chain [22, 23], which leads to a decrease in oxidative metabolism and, consequently, to an increase in anaerobic respiration and lactate secretion [23].

Metformin has also been reported to be valuable as a protective compound in the supplementation of sperm cryopreservation media [24]. Cryopreservation is a method routinely used to conserve male spermatozoa for, among others, bypassing infertility issues [25]. However, this technique may cause permanent damage to spermatozoa such as loss of motility, reduced DNA integrity, and apoptosis [26]. Not only exposure of fresh semen to metformin did not induce negative effects on spermatozoa quality, as the addition of this drug to the cryopreservation protocol led to an improvement in the fertilization rates and a reduction in the percentage of abnormal zygotes after in vitro fertilization [24].Thus, metformin is being regarded as a potential additive to cryopreservation media since it presents beneficial effects in improving the quality of frozen semen.

In sum, although data from studies involving human individuals or human material are scarce, it is generally accepted that metformin improves several aspects in the reproductive function of diabetic individuals. Metformin is one of the most prescribed anti diabetic drugs, but its effects on male fertility have been lightly investigated. It is imperative to fully scrutinize the molecular mechanisms behind the effects of metformin on the overall human male reproductive function, and those that may individually affect testicular cells, spermatogenesis, sperm production and sperm maturation. Definitely, as fertility rates dramatically decrease, the relevance of studying the influence of drugs that protect the male reproductive function exponentially increases.

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