International Journal of Diabetology & Vascular Disease Research (IJDVR)
ISSN: 2328-353X

The Antidiabetic Drug Metformin and Male Fertility: An Update

Editorial

João C. Ribeiro[1], Marco G. Alves[1], Pedro F. Oliveira[1,2,3*]

[1] Department of Microscopy, Laboratory of Cell Biology, Institute of Biomedical Sciences Abel Salazar (ICBAS) and Unit for Multidisciplinary Research in Biomedicine (UMIB), University of Porto, Porto, Portugal.
[2] Department of Genetics, Faculty of Medicine, University of Porto, Porto, Portugal.
[3] Institute of Research and Innovation in Health (i3S), University of Porto, Portugal.

Abbreviations: LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone.

Diabetes *mellitus* is a chronic disease with pandemic proportions. It has been estimated that 451 million people were diabetic in 2017 and recent statistics suggest that a worrisome 693 million people will suffer from diabetes in 2045 [1]. This metabolic disease is defined by impaired plasma glucose levels [2], which is due to insufficient insulin secretion or/and insulin resistance [3]. Thus, diminished insulin bioactivity causes a dysregulation on glucose metabolism in multiple tissues and, if not properly treated, hyperglycaemia and low insulin levels can evolve to other conditions and co-morbidities of distinct nature [4].

Pharmacological agents with antidiabetic activity have the ability to balance the dysregulated glycolytic flux on diabetics. Multiple drugs have this regulatory effect, among which metformin stands out as one of the most prescribed antidiabetic drugs. In fact, metformin was one of the first antidiabetic drugs discovered and is widely used. This biguanide is able to inhibit liver gluconeogenesis [5] which is the main antidiabetic property of this compound. However, this drug also stimulates glucose transporters, promoting glucose internalization [6], and reducing glycaemia levels.

Pharmacological treatment and lifestyle changes are crucial for minimizing the impact of diabetes *mellitus* on the metabolism of multiple organs. One of the most neglected systems affected by this pathology is the male reproductive system [7]. It has been reported that the diabetic condition dysregulates spermatogenesis [8] and can cause erectile dysfunction [9], among others. Both factors impair male fertility and impact life quality of male diabetic patients. Interestingly, studies on metformin treatment made in healthy rats showed a negative impact on male fertility [10]. Treatment with 30 mg/kg of metformin during 21 days showed to decrease testosterone and sperm count levels. On the other hand, treatment of diabetic rats with doses of 100 mg/kg of this biguanide for 4 weeks was able to reverse the negative effects of diabetes on fertility by restoring testosterone levels and seminiferous tubules physiology [11]. An overview of this subject has been published by Meneses and colleagues, in 2015. The authors presented and discussed the available data regarding the effects of metformin on male reproductive function [12]. Herein, we will update this subject based on literature published since then and by discussing the new results available.

Spermatogenesis is regulated by the hypothalamus-pituitary-testis axis, via the secretion of two major pituitary hormones: the luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts in Leydig cells, activating the synthesis of androgens that are a critical element for spermatogenesis development [13]. Metformin decreases testosterone levels in healthy male rats, however this biguanide restores testosterone secretion in diabetic rats to levels near those seen on healthy individuals [14]. A recent study, associated these effects with the modulation of testicular proteins responsible for steroidogenesis (StAR and CYP11A1). The mRNA transcripts levels of these proteins were increased when streptozotocin-induced diabetic rats were treated with 300 mg/kg of metformin for 4 weeks [14], which resulted in augmented levels of testosterone. On the other side, FSH is equally important for male fertility, since it has an important role on Sertoli cell proliferation [13], through the stimulation of cyclin expression [15]. In an experiment with rat Sertoli cells, 24 hours treatment with 10 mM of metformin showed to decrease mRNA levels of cyclin *D1* and *D2*, which led to a decrease in Sertoli cell population, when compared with non-treated animals [15]. The authors hypothesized that metformin

***Corresponding Author**:
Pedro F. Oliveira,
Department of Microscopy, Laboratory of Cell Biology, Institute of Biomedical Sciences Abel Salazar (ICBAS) and Unit for Multidisciplinary Research in Biomedicine (UMIB), University of Porto, 4050-313 Porto, Portugal.
E-mail: pfobox@gmail.com

Received: February 04, 2019
Published: February 07, 2019

Citation: João C. Ribeiro, Marco G. Alves, Pedro F. Oliveira. The Antidiabetic Drug Metformin and Male Fertility: An Update. *Int J Diabetol Vasc Dis Res.* 2019;7(1e):1-3.
doi: http://dx.doi.org/10.19070/2328-353X-1900014e

seemed to have an opposite effect to FSH on the proliferation of Sertoli cells on non-diabetic individuals. In fact, metformin is known for decreasing cell proliferation and having application on cancer cells containment [16]. However, despite 10 mM of metformin for 24h decreased Sertoli cell number, this treatment did not affect remaining testicular cells [15] or sperm viability [17]. In a similar study, using prepubertal chicken Sertoli cells, metformin induced a similar decrease in Sertoli cells number, without affecting apoptosis rate or cell viability. The authors also suggested that metformin seemed to delay the development of germ cells [18], based on the alterations detected on seminiferous tubules physiology, which can be considered as a red flag for male reproductive function impairment. These negative results are seemingly caused by the fact that the experiment was performed in non-diabetic animal models. With this in mind, Tertti and co-workers designed an experiment where they studied if treatment with 1500 mg/day of metformin during pregnancy in humans with gestational diabetes could affect the male offspring fertility [19]. The trial was performed in pregnant women with 22 to 34 weeks of gestation and the testicular size of male offspring, with ages between 33 to 85 months, was measured. This study did not detected any difference in testicular size between the offspring of moms treated with metformin, and treated with insulin. However, in a similar study performed in rats, the male offspring of treated mothers between the first gestation day and the twenty first lactation day with metformin 300 mg/kg/day showed a decrease in sperm count [20]. In addition, the sexual behaviour of offspring from rats treated and not treated with metformin were distinct. The offspring of treated rats recorded a larger number of intromissions necessary to ejaculation and a smaller latency to the first intromission. The author hypothesised that the observed results on sexual behaviour caused by metformin, could be mediated by the ability to impair sex hormone-binding globulin secretion levels and the fact that metformin can act as an aromatase inhibitor [20]. Both factors resulted in lower testosterone bioactivity, which led to lower sexual appetite. It is worth to highlight, like in the experiment made in humans, the authors did not found any difference on testicular weight between the two experimental groups.

Ghasemnejad-Berenji and co-workers performed a study where the protective effect of metformin on rats that were physically damage by torsion and detorsion of the testis was accessed. Metformin showed to be relevant to maintain a well-organized structure of seminiferous tubules, while intratubular necrosis and a lower number of germ cells were observed in non-treated rats [21]. Metformin treatment resulted in increased epididymal sperm concentration and sperm motility, mainly by the reduction of oxidative stress and apoptosis of germ cells. From these novel studies we can conclude that metformin has a protective effect not only on sperm but also on testicular cells, especially on intratubular tissue, which leads to a normalization of spermatogenesis.

Altogether, the available data on the effects of metformin on male fertility highlights an enhanced reproductive function when used on diabetic patients. However, these results contrast with those described in healthy males and in the male offspring of treated animals. An increasing number of studies is continuously providing new questions, which ultimately will produce more data regarding the effect of metformin on male fertility. Metformin continues to be one of the most prescribed antidiabetics in the world and, particularly due to the declining fertility rates and the fertility problems associated with type 2 diabetes *mellitus*, the importance of the studies accessing the impact of metformin on testicular cells metabolism, spermatogenesis, and sperm maturation is clearly increasing.

References

[1]. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018 Apr;138:271-281. doi: 10.1016/j.diabres.2018.02.023. PubMed PMID: 29496507.

[2]. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes--2018. Diabetes Care. 2018 Jan;41(Suppl 1):S55-S64. doi: 10.2337/dc18-S006. PubMed PMID: 29222377.

[3]. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes--2018. Diabetes Care. 2018 Jan;41(Suppl 1):S13-S27. doi: 10.2337/dc18-S002. PubMed PMID: 29222373.

[4]. Meneses MJ, Silva BM, Sousa M, Sá R, Oliveira PF, Alves MG. Antidiabetic Drugs: Mechanisms of Action and Potential Outcomes on Cellular Metabolism. Curr Pharm Des. 2015;21(25):3606-20. PubMed PMID: 26166608.

[5]. Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, DePinho RA, et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science. 2005 Dec 9;310(5754):1642-6. PubMed PMID: 16308421.

[6]. Pernicova I, Korbonits M. Metformin--mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol. 2014 Mar;10(3):143-56. doi: 10.1038/nrendo.2013.256. PubMed PMID: 24393785.

[7]. Ferreira C, Rabaca A, Sousa M, Oliveira P, Alves M, Sa R. Impact of Metformin on Male Reproduction. Curr Pharm Des. 2015;21(25):3621-33. PubMed PMID: 26166607.

[8]. Alves MG, Socorro S, Silva J, Barros A, Sousa M, Cavaco JE, et al. In vitro cultured human Sertoli cells secrete high amounts of acetate that is stimulated by 17beta-estradiol and suppressed by insulin deprivation. Biochim Biophys Acta. 2012 Aug;1823(8):1389-94. doi: 10.1016/j.bbamcr.2012.06.002. PubMed PMID: 22705155.

[9]. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care. 2007 Apr;30(4):911-7. PubMed PMID: 17392552.

[10]. Adaramoye O, Akanni O, Adesanoye O, Labo-Popoola O, Olaremi O. Evaluation of toxic effects of metformin hydrochloride and glibenclamide on some organs of male Rats. Niger J Physiol Sci. 2012 Dec 18;27(2):137-44. PubMed PMID: 23652227.

[11]. Nasrolahi O, Khaneshi F, Rahmani F, Razi M. Honey and metformin ameliorated diabetes-induced damages in testes of rat; correlation with hormonal changes. Iran J Reprod Med. 2013 Dec;11(12):1013-20. PubMed PMID: 24639728.

[12]. Meneses MJ, Sousa M, Alves MG, Oliveira PF. The Antidiabetic Drug Metformin and Male Reproductive Function: An Over-view. Int J Diabetol Vasc Dis Res. 2015 Apr 20;3:1-2.

[13]. Alves MG, Rato L, Carvalho RA, Moreira PI, Socorro S, Oliveira PF. Hormonal control of Sertoli cell metabolism regulates spermatogenesis. Cell Mol Life Sci. 2013 Mar;70(5):777-93. doi: 10.1007/s00018-012-1079-1. PubMed PMID: 23011766.

[14]. Nna VU, Bakar ABA, Ahmad A, Mohamed M. Down-regulation of steroidogenesis-related genes and its accompanying fertility decline in streptozotocin-induced diabetic male rats: ameliorative effect of metformin. Andrology. 2018 Dec 4. doi: 10.1111/andr.12567. PubMed PMID: 30515996.

[15]. Rindone GM, Gorga A, Regueira M, Pellizzari EH, Cigorraga SB, Galardo MN, et al. Metformin counteracts the effects of FSH on rat Sertoli cell proliferation. Reproduction. 2018 Aug;156(2):93-101. doi: 10.1530/REP-18-0233. PubMed PMID: 29789441.

[16]. Mitsuhashi A, Kiyokawa T, Sato Y, Shozu M. Effects of metformin on endometrial cancer cell growth in vivo: a preoperative prospective trial. Cancer. 2014 Oct 1;120(19):2986-95. doi: 10.1002/cncr.28853. PubMed PMID: 24917306.

[17]. Hurtado de Llera A, Martin-Hidalgo D, Garcia-Marin LJ, Bragado MJ. Metformin blocks mitochondrial membrane potential and inhibits sperm motility in fresh and refrigerated boar spermatozoa. Reprod Domest Anim. 2018 Jun;53(3):733-741. doi: 10.1111/rda.13164. PubMed PMID: 29602187.

[18]. Faure M, Guibert E, Alves S, Pain B, Rame C, Dupont J, et al. The insulin sensitiser metformin regulates chicken Sertoli and germ cell populations. Reproduction. 2016 May;151(5):527-38. doi: 10.1530/REP-15-0565. PubMed PMID: 26917452.

[19]. Tertti K, Toppari J, Virtanen HE, Sadov S, Ronnemaa T. Metformin Treatment Does Not Affect Testicular Size in Offspring Born to Mothers with Gestational Diabetes. Rev Diabet Stud. 2016 Spring;13(1):59-65. doi: 10.1900/RDS.2016.13.e2015013. PubMed PMID: 26859658.

[20]. Forcato S, Novi D, Costa NO, Borges LI, Goes MLM, Ceravolo GS, et al. In utero and lactational exposure to metformin induces reproductive alterations in male rat offspring. Reprod Toxicol. 2017 Dec;74:48-58. doi: 10.1016/j.reprotox.2017.08.023. PubMed PMID: 28867217.

[21]. Ghasemnejad-Berenji M, Ghazi-Khansari M, Yazdani I, Nobakht M, Abdollahi A, Ghasemnejad-Berenji H, et al. Effect of metformin on germ cell-specific apoptosis, oxidative stress and epididymal sperm quality after testicular torsion/detorsion in rats. Andrologia. 2018 Mar;50(2). doi: 10.1111/and.12846. PubMed PMID: 28730645.