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Effect of metformin on semen quality

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Various studies have linked metformin, a universally antidiabetic drug, with semen quality; however, such a direct link has not been established. This review systematically addresses and summarizes the effect of metformin on semen quality, particularly sperm function. We searched the MEDLINE electronic database for English articles and abstracts containing the key words 'metformin' and 'sperm', and relevant articles were reviewed. In summary, metformin appears to have improved and provided positive impact on sperm quality. This effect may be due to the ability of metformin to reduce oxidative stress and lipid peroxidation, enhance 5'-AMP activated protein kinase activity, and restore the normal levels of pituitary-gonadal hormones. However, further clinical research is still necessary to confirm such effect.

Uniterms: Metformin/effects. Metformin/review. Metformin/semen quality. Sperm/study. Testosterone. Oxidative stress. 5'-AMP activated protein kinase.

INTRODUCTION

Metformin, a biguanide-derivative antidiabetic drug, is the most widely used oral agent in humans (Brinkmann, Brixius, 2015; Chhetri, Thapa, Van Schepdael, 2014). It is the first-line drug for the treatment of type 2 diabetes, particularly, in overweight and obese patients with normal kidney function (American Diabetes, 2009; George, Joseph, 2014; Hung *et al.*, 2015). In addition, recent research has proposed that metformin alone or in combination with insulin may be safe to treat gestational diabetes and does not increase the risk of metabolic acidosis (Huang, Castelino, Peterson, 2015; Kitwitee *et al.*, 2015). Metformin's mechanism of action involves suppression of hepatic gluconeogenesis (Ferrannini, 2014; Foretz *et al.*, 2010; Todd, Florez, 2014). One concern that has been raised relevant to metformin usage is that the consensus panel of diabetes felt that metformin should be considered for diabetes prevention even in non-diabetic individuals (i.e., pre-diabetic or obese individuals). This concern increases the use of this drug by these groups (American Diabetes, 2009; Hostalek, Gwilt, Hildemann, 2015; Manu *et al.*, 2015; McGavock, Dart, Wicklow, 2015).

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Over the last decade, various experimental and clinical studies have linked metformin with sperm function, and thus with male factor infertility (Alves *et al.*, 2014; Ferreira *et al.*, 2015); however, such direct link has not been established. In this review, we provide fresh and comprehensive understanding of the effect of metformin, as a universally used oral agent, on semen quality (i.e., sperm quantity and quality). To do this, we searched the MEDLINE electronic database for English-language articles and abstracts reported using the key words 'metformin' and 'sperm'. The references from selected articles were reviewed and used if relevant.

Effect of metformin on sperm parameters

Positive effects

To date, the majority of studies linking metformin to sperm parameters are nonclinical. In his study on streptozotocin-induced diabetic rats, Attia, Helal, Alhaider (2009) made the seminal observation that metformin decreases the diabetes-induced genomic instability and cell proliferation changes in germinal cells in a dose-dependent manner (2500, 500, >100 mg/kg) (Attia, Helal, Alhaider, 2009). Later in vivo system study on diabetic rats clearly showed that oral treatment with metformin (50 mg/kg/day, for 4 weeks) in combination with pioglitazone, another antidiabetic drug, at 1 mg/kg increases the caudal sperm count and decreases sperm morphology defects

(Rabbani, Devi, Khanam, 2010). Moreover, epididymal sperm count, motility, and morphology were improved in diabetic rats upon treatment with metformin at 30 mg/kg/day for 6 weeks (Adaramoye, Lawal, 2014). Furthermore, diet-induced obesity rats fed orally with metformin for 12 weeks had higher epididymal sperm count and motility (Fang *et al.*, 2012).

Further, a number of in vitro studies have revealed positive effects of metformin on sperm parameters. Adding metformin at 50 μM to cryopreservation media of mouse semen improved the quality (motility and morphology) of frozen sperm (Bertoldo *et al.*, 2014). A recent study conducted by Nguyen *et al.* (2014) showed that metformin enhances chicken sperm motility and viability, and increases acrosome reaction and lactate production (Nguyen *et al.*, 2014).

The clinical study that displays the effect of metformin on sperm parameters was recently conducted by Bosman *et al.* (2014) on hyperinsulinaemic men (Bosman *et al.*, 2014). This group showed that administration of metformin at the therapeutic dose improves sperm morphology (from 3.9% to 5.5%) and enhances chromatin packaging quality by about 8.3% (Bosman *et al.*, 2014).

Negative effects

Until now, only few reports have displayed negative effects of metformin on semen quality. Oral treatment of male rats with metformin at 30 mg/kg/day for 3 weeks decreased epididymal sperm count and motility by 34% and 31%, respectively; while sperm live/dead ratio did not change using this treatment (Adaramoye *et al.*, 2012). An *in vitro* study conducted by Adaramoye *et al.* (2012) to determine the toxic effects of metformin on mouse sperm observed a slight decrease in sperm motility when using high concentrations of metformin (5000 μM); while using low concentration (50 μM) of metformin did not induce any change in sperm quality (i.e., count, motility) (Bertoldo *et al.*, 2014).

Studies on the pharmaceutical action of metformin

Positive effects

The mechanisms by which metformin induces the positive effects on sperm quality have been explained in a number of published articles. One obvious mechanism is that metformin reduces the level of oxidative stress (Banihani *et al.*, 2014), an imbalance between oxidants and antioxidants to the favor of the former, and lipid peroxidation (Attia, Helal, Alhaider, 2009). It has been shown that metformin supplementation at 30 mg/kg restores the antioxidant function such as reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase, and glutathione-S-transferase in diabetic male rats (Adaramoye, Lawal, 2014). Similar findings of enhancing the antioxidant function were observed when using diet-induced obesity rats (i.e., higher superoxide dismutase and glutathione peroxidase, and lower malondialdehyde) (Fang *et al.*, 2012). In fact, metformin was identified as having antioxidant activity against oxidative damage by reactive oxygen species (Cahova *et al.*, 2015; Ouslimani *et al.*, 2005).

Moreover, metformin was found to enhance the phosphorylation of 5'-AMP activated protein kinase (AMPK), which is a sensor protein of cellular energy status, thus, a strategic enzyme in regulating energy balances (i.e., glucose and lipid metabolism) (Bertoldo *et al.*, 2015; Hardie *et al.*, 2003; Ma *et al.*, 2015; Nguyen *et al.*, 2014, 2015). Therefore, metformin may improve sperm function via enhancing the activity of AMPK.

Furthermore, some in vivo system studies have discussed the effect of metformin on pituitary-gonadal hormones. The study conducted by Adaramoye and Lawal (2014) on diabetic male rats showed that metformin is able to restore follicle-stimulating hormone, leutinizing hormone, and testosterone (Adaramoye, Lawal, 2014). Likewise, oral administration of metformin succeeded to restore testosterone level back to normal in diabetic rats (Ayuob, Murad, Ali, 2015).

Negative effects

In contrast, the clinical study conducted by Ozata *et al.* (2001) concluded that metformin use in combination with a hypocaloric diet decreases free testosterone and sex-hormone-binding globulin levels in nondiabetic obese men, and decreases total testosterone levels in obese patients with type 2 diabetes (Ozata *et al.*, 2001).

CONCLUSIONS AND FUTURE PERSPECTIVES

To date, the mainstream of research is presenting positive effects of metformin on semen quality and sperm function, though there will still few reports that have deliberated some negative effects. Consequently, metformin, typically at the therapeutic dose, appears to be encouraging when considering its direct effect on semen quality and sperm function. Such effect may be due to the ability of metformin to reduce the oxidative damage and lipid peroxidation, enhance AMPK activity, and restore the normal levels of pituitary-gonadal hormones. While, with further studies, mainly clinical, are still of great importance to confirm these effects. Our laboratory is

currently running a clinical study, using flow cytometry, to standardize the favorable and unfavorable concentrations of metformin to human sperm, particularly to the DNA of human sperm.

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