



## Research Article

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### *Review on Metformin Effect on Male Reproductive System*

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#### ABSTRACT

*Male infertility and issues of impaired fecundity have been currently a global problem. Diabetes mellitus can influence male fertility either directly or indirectly due to abnormal spermatogenesis, which results in reduced sperm quality. Most reported cases of diabetes are of type 2 DM cases, frequently treated with oral anti-diabetic drugs. Metformin is considered first-line therapy for the treatment of T2DM. This drug is an oral insulin-sensitizing agent that can elevate insulin sensitivity and reduce plasma fasting insulin. The main metabolic action of metformin target the liver. However, it was indicated that metformin acts on many organs of the body which include the male reproductive system. With the increasing numbers of diabetic individuals among younger people, there is an enhancement in the utilization of metformin in individuals of this age group. Therefore, it is critical to recognize the role of metformin in male fertility. In this review, we are presented with the most recent data accessible regarding the investigation of the influences of metformin on the male reproductive system. Together with the discussion of these influences, their importance to male fertility is also argued.*

**Key words:** *Metformin, Oral Hypoglycemic Agents, Diabetes mellitus, Fertility, Erectile Dysfunction, Reproductive system.*

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#### INTRODUCTION

Diabetes is one of the primary causes of mortality [1], morbidity, and long-term health issues worldwide [2]. Diabetes Mellitus (DM) is a complex metabolic disorder [3] concerned with hyperglycemia caused by the absence of insulin secretion, impaired insulin action, or both, which is associated with severe impairment in the metabolism of carbohydrates, fats, and proteins [4]. Diabetes Mellitus is a global epidemic illness influencing over 400 million adults worldwide, and unfortunately, it is expected to increase to over 600 million in 2040 [4].

There are two main sorts of diabetes mellitus; type 1 diabetes is caused by an absolute shortage of insulin secretion; whereas in the other, which is more prevalent, type 2 diabetes is produced by a mixture of resistance to insulin action and inadequate insulin secretion [5].

The number of DM type II cases among the age group of 20-74 years in Yazd was 21.4 per 1000 of a population per year. The analysis showed that there are many risk factors of DM like smoking, increasing body mass index, increased waist circumference, high blood pressure, and raised triglyceride, cholesterol, and uric acid levels [6]. A high body mass index (BMI) contributes less to the increased risk of T2D than the increased visceral obesity, and/or ectopic fat (liver fat) [7].

Regular consumption of sweetened beverages is somewhat associated with weight-gain and considered to be a risk factor of T2DM and cardiovascular disease [8]. Although smoking is identified to reduce body weight, it is correlated with central obesity, also rises inflammation and oxidative stress, and  $\beta$ -cell destruction [9].

Patients with type two diabetes mellitus have an enhanced mortality and morbidity rate compared with non-diabetics and are more probable to develop coronary artery, cerebrovascular, and peripheral vascular illnesses [10].

Some studies showed that intensified oxidative stress which is following elevated blood glucose implicated in creating diabetes complications, lowering serum concentration of testosterone besides the negative impact on the reproductive system like reduction in accessory sex glands weight, reducing sperm content in the epididymis and increasing basement membrane thickness is reported in diabetic patients [11].

The effects on the human vascular tree -directly or indirectly- are the major source of morbidity and mortality in both type one and type two diabetes. Usually, the harmful influences of hyperglycemia are classified into macrovascular complications (heart disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) [12], in both types 1 and 2 DM, improved blood glucose level will decrease the progression of diabetic retinopathy, and duration of diabetes is considered to be noteworthy risk factors [13].

### Oral Hypoglycemic Agents

In patients with type 2 diabetes, pharmacological treatment should be started when glycemic control is not reached or if HbA1C rises to 6.5% after 2–3 months of lifestyle modification [14], Criteria for initiation of therapy with an oral agent versus insulin are discussed among diabetologists, but the decision should be taken by the specialist and patient to obtain the optimum results [15].

Biguanides classes like metformin acting by inhibiting hepatic gluconeogenesis mostly through potentiating the impact of insulin, decreasing hepatic extraction of certain substrates like (lactate), and reverse the influences of glucagon. Similarly, metformin can reduce the rate of glycogenolysis and lowering the influence of hepatic glucose-6-phosphatase. Insulin-stimulated glucose uptake into skeletal muscle is supported by metformin [16], Its popularity originates from its capacity to lower blood glucose without inducing hypoglycemia or weight gain while maintaining an exceptional safety profile [17]. Metformin may accumulate when renal function is insufficient because it is excreted by the kidneys [18].

Sulfonylureas class like Glyburide, glipizide, glimepiride, tolazamide, and tolbutamide, sulfonylureas exert its action by enhancing peripheral glucose use through two mechanisms of action, by stimulating hepatic gluconeogenesis, and by increasing the number and sensitivity of insulin receptors decrease hepatic glucose output, and increase insulin receptor sensitivity at peripheral target tissues [19].

For treating type 2 diabetes, thiazolidinedione (TZD) is a very strong insulin sensitizer, Restoration of insulin sensitivity is a dominant strategy for treating type 2 diabetes [20].

Alpha Glycosidase inhibitors inhibit many alpha-glucosidase enzymes like (maltase), consequently retarding the absorption of sugars from the gut [21].

Meglitinides are insulinotropic agents, released in 1995 and approved for clinical utilization in adults with non-insulin-dependent diabetes in 2000. They are insulin secretagogues molecules, faster hypoglycemic action, and shorter duration of action in contrast with sulfonylureas, thus come up with better control of postprandial hyperglycemia and reduction of the risk of late hypoglycemia [22].

Dipeptidyl-peptidase-4 (DPP-4) inhibitors such as Linagliptin, Saxagliptin, Sitagliptin, and Alogliptin, indicate a group of oral hypoglycemic agents that block the inactivation of the “incretin” hormones, namely glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), and therefore influence glucose control by numerous procedures, including improvement of glucose-dependent insulin secretion, decelerated gastric emptying, and lessening of postprandial glucagon and food intake [23].

### Fertility

The capability to establish a clinical pregnancy is recognized as fertility [24]. Infertility is explained as the incapability to get pregnant after one complete year of regular, unprotected sexual intercourse [25]. It can also be expressed as the failure of a couple to conceive after 1 year of regular sex without the intrusion of contraception in women <35 years.

### Effect of Drugs on Fertility

Infertility may result from the use of many drugs. This occurrence may be the consequence of an influence on the hypothalamic-pituitary-gonadal axis or a direct toxic impact on the gonads [26].

Metformin was a promotive drug for fertility particularly in females, shown to increase fertility consequences in females with insulin resistance correlated with polycystic ovary syndrome (PCOS) and in obese males with decreased fertility. Metformin controls the menstrual cycle, reduces the occurrence rate of cesareans, and lower the number of premature births [27].

Beta-blockers and calcium-channel blockers (CCBs) appear to play a main role on male fertility, resulting in different cases of azoospermia and/or oligozoospermia, CCBs, like amlodipine, can lessen testosterone level, luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels, leading to influence on spermatogenesis and sperm parameters [28].

Research has suggested that non-steroidal anti-inflammatory drugs (NSAIDs) therapy is associated with human infertility, thus, inhibit ovulation in all mammalian species examined so far, likely because of the blockage of cyclooxygenase 2, the inducible isoform of cyclooxygenase (COX), that is the rate-limiting enzyme in prostaglandin synthesis. COX-2 inhibition plays a key role in ovulation, fertilization, and implantation [29]. Besides, chemotherapy treatments can result in ovarian failure. Histological investigations in human ovaries have revealed that chemotherapy treatments can cause loss of primordial follicles and ovarian atrophy [30]. Numerous investigations have recommended that recreational drugs might affect human reproductive health adversely. Cannabis smoking damages male fertility, with an influence on the hypothalamus-pituitary-gonadal axis, sperm synthesis, and sperm activity, as cannabinoid receptors are expressed in the anterior pituitary, Leydig cells, Sertoli cells and in testicular cells [31].

Sulfasalazine an anti-inflammatory drug which often prescribed for patients with rheumatoid arthritis and had been used for the initial treatment of irritable bowel illness and long-term maintenance of disease remission. Levi et al. first noted 4 cases of male infertility related to sulfasalazine use in 1979, and in all cases, success to conceive after discontinuation of sulfasalazine drug. Subsequent studies stated that this medication causes reversible non-dose-dependent quantitative and qualitative deformities of sperm in > 80% of men [32].

Anabolic steroids - often taken by bodybuilders and athletes, these, particularly after long term utilization can seriously decrease sperm count and mobility. A study on sperm parameters indicated that based on the duration of the utilization of anabolic steroids and the time since the last drug administration before the survey, it concluded that bodybuilders have lower percentages of motile sperm in compare to the healthy participant, but sperm production can return to normal rates after stopping the consumption of anabolic steroids [33].

Another risk factor for infertility is age; some investigations said that fecundity in females starts to reduce during the 4th decade of life [34].

It is known that smoking has a damaging influence on fertility from long ago. In 1983, Osler, together with his working group found that Tobacco consumption caused infertility in about a thousand females where no other factor was found [35]. Alcohol consumption may lower male fertility, besides the established knowledge that alcohol consumption causes significant changes in spermatozoon shape; among which are the spermatozoon head's cleavage, curling of tails, and mid-portion distension, it is also thought of to manipulate spermatogenesis as well as the secretion of testosterone. It is found that, in the alcoholic population, azoospermia follows spermatids degeneration in the seminiferous tubules which was found in turn to be due to changes in the hormonal axis controlling testicular function and/or male's accessory glands [36].

Being obese or overweight - found to be the principal cause of female infertility, in obese women, gonadotropin secretion is affected because of the increased androgens peripheral conversion to estrogens. In obese women, insulin resistance and hyperinsulinemia may lead to hyperandrogenemia. The sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP) are reduced and leptin levels are enhanced. This deranges the hormonal axis that controls the gonads [37].

### Effects of Diabetes Mellitus on male fertility

Diabetes-related sperm nuclear and mtDNA damage decrease diabetic men reproductively [38]. Both T1DM and T2DM influence the testicular function and spermatogenesis [39]. At the electron microscopic level sperm motility was also meaningfully decreased, sperm from diabetics patient displayed more immaturity- and apoptosis-associated abnormality [40]. Analysis of the ejaculate, using light microscopy, showed minimal effect on semen quality. The molecular analysis on the other hand demonstrated that diabetic men have a significant DNA fragmentation and pointed out that oxidative damage is the cause [39]. It is reported that the sperm DNA

diabetes – caused damage will negatively affect the quality of embryo as early as the second day of early embryonic development, this would then continue as the embryo is transferred, lead to higher abnormality rates at implantation and negative outcomes [41].

Men with diabetes may be at high risk of low testosterone levels and reduced sex steroid status [42], diabetes affects penile tissues differently as a result of cellular heterogeneity. These changes could have an impact on blood flow and tissue resistance, and therefore might adversely affect erection which leads to retardation of ejaculation ability [43]. Diabetes also causes impaired relaxation of cavernosal smooth muscle due to nitric oxide (that is derived from the endothelium), this may be a side effect of glycosylation products [44], and the occurrence of Erectile Dysfunction in men with diabetes is about three-fold higher than in the general population as it is correlated with diabetic neuropathy and peripheral vascular disease [45], as it may also be the presenting symptom for DM and may predict later neurologic sequelae [44].

#### **Effect of oral hypoglycemic agents on male fertility :**

The study of sulfonylurea's effect on the fertility parameter stated that it is highly possible when using sulfonylurea as a primary treatment of diabetes to restore total serum testosterone levels together with testosterone secretion index values in T2DM men in their middle-age [46].

According to study on glucagon-like peptide 1 (GLP1) effect on fertility of obese mice, it stated that Exenatide reduced total body weight but not reproductive organs weight, as it improved the basic sperm parameters, improved the reduced sperm mitochondrial activity, recovered the impaired sperm integrity and up-regulated the expression of GLP-1R in testis [47].

Rabbani et al. (2008) assessed the role of Pioglitazone (PIO) and Rosiglitazone (RSG) on the rate of nuclear and germinal cell damage by utilizing sperm shape abnormality, bone marrow micronucleus (MN) test, and sperm count in normal animals. They noted that RSG lessened the P/N (polychromatic and normochromic erythrocytes) ratio at 10 and 100 mg/kg without revealing influence on the rate of micronucleated erythrocytes, sperm shape morphology, and sperm count. P/N ratio and sperm count tend to modify with a greater dose (100 mg/kg) of P/O than the tested doses and demonstrated lessened MN in normochromic erythrocytes and percentage of sperm morphological abnormality in comparison with the control group [48].

A research assessed the influence of acarbose on the fertility of STZ-induced diabetic rats, it was observed, that the reduction on the numbers of spermatogonial cells, spermatocytes and Sertoli cells in the testis was lower in the diabetic rats treated with acarbose than that detected on untreated diabetic rats, so it concluded that acarbose has positive effect toward male fertility [49].

In one study of a case report, stated that the semen quality of the patient deteriorated sharply following three-month Dipeptidyl peptidase –IV inhibitor (DPP-IV I) administration. Semen quality recovered after the drug is withheld; subsequently, the DPP-IV inhibitor was re-instituted. The quality of the semen deteriorated again but, fortunately, it was recovered after the drug withdrawal. Semen quality deterioration cause remains largely unknown; in this clinical course, it is suggested that DPP-IV inhibitor may affect spermatogenesis. So that, in young adults, treatment with DPP-IV inhibitor warrants careful attention when it is administered [50].

It is stated that insulin-dependent male diabetics have enhanced semen volume, sperm count, and morphology. But, sperm motility was better in metformin users than insulin users. Nevertheless, both insulin and metformin utilization insignificantly influence serum testosterone levels in the diabetics. Consequently, metformin might play a better role than insulin in the improvement of sperm motility in the diabetic male population [51].

#### **Metformin effect on male fertility**

Metformin belongs to the biguanides group which is old agents utilized for patients with non-insulin-dependent diabetes mellitus (NIDDM) that acts by decreasing hepatic glucose output and, to a lesser extent, enhancement of the insulin sensitivity in hepatic and peripheral tissues [52]. The drug considered of choice in the treatment of type two diabetes mellitus is Metformin. This has long been considered so. The clinical guidelines most widely recognized and the consensus recommendations prefer its use was monotherapy initially for hyperglycemia [53]. As it enhances peripheral sensitivity to insulin, it exerts decreases in hepatic glucose production, reduces the absorption of glucose in the gut, and enhances peripheral glucose uptake and utilization [54].

The commonest Metformin side effects (affect 10% of patients few days into treatment) are gastrointestinal, including mild loss of appetite, and a metallic taste, nausea, abdominal discomfort, and diarrhea [55]. Slow-dosage titration is suggested to lessen these influences, and should be started at 500 mg twice daily with meals, and can be enhanced by 500 mg (maximum dosage of 2,000 mg daily) at two-week intervals to decrease gastrointestinal

side effects. A novel extended-release formulation was newly presented to the market, permitting a more convenient once-daily dosing regimen [56].

Metformin is the first-line treatment for type 2 diabetes, mainly, in overweight and obese patients with normal kidney function; a related concern that has been raised was its usage in non-diabetics for primary inhibition of diabetes (i.e., pre-diabetic or obese individuals). This concern rises the usage of this drug by these groups [57].

Metformin is extensively applied as first-line therapy for the treatment of type 2 diabetes accompanied by lifestyle modification because of its efficiency and low side effect profile. Metformin monotherapy is predictable to lower the HBA1c by 1.0-2.0%. There are only a few conditions in which metformin should not be utilized, including chronic kidney disease and gastrointestinal intolerance [58].

Metformin is a hydrophilic biguanide compound with high polarity, positively charged, and has low molecular weight with pleiotropic actions. It extensively accumulates in some tissues including the liver, pancreas, muscle, adipose tissue, pituitary, hypothalamus, and the gonads [59].

Numerous experimental and clinical studies over the last decade, have linked it to male infertility since it influences sperm function [57]; however, such a direct link yet to be established. In this review, we provide a comprehensive and fresh understanding of the influence of metformin, as an oral agent utilized universally, on male fertility and gonadal hormones.

### **Effect of Metformin on rat testis**

Metformin has a strong Protective effect on testicular ischemia and reperfusion injury in rats, as ischemic reperfusion reduced the activities of superoxide dismutase (SOD) enzyme and testicular Johnsen's scores together with an elevation in myeloperoxidase (MPO) as well as malondialdehyde (MDA) levels, metformin had restored testicular Johnsen's scores, SOD activity, MPO and MDA levels [60].

Increasing body weight fits in reverse with testis weight, clear pathological modifications in the testicular tissue were characterized by small, atrophic, and distorted seminiferous tubules and destroyed basement membrane, Metformin treatment improved the semen profile, this might be due to weight loss that it promotes. Reduced testicular cell apoptosis and enhanced testicular weight by metformin resulted in the correction of the metabolic disorder and restoration of hormonal [61].

Metformin for T2DM male patients in reproductive age can be considered as an appropriate oral hypoglycemic ant diabetic drug, as some investigations noted that it decreases Sertoli Cells' mRNA amount and levels of proteins for glycolysis-associated transporters but enhances their activity; and induces antioxidant activity by stimulating alanine production and maintains the NADH/NAD<sup>+</sup> equilibrium. Metformin enhances lactate levels in SCs thereby providing the nutritional support and it also provides anti-apoptotic influences in developing germ cells [62].

As stated in many investigations in diabetic induced rats, diabetes mellitus leads to significantly ultrastructural modifications of Sertoli and Leydig cells that cause changes in pituitary-derived gonadotropins, and these modifications, in turn, influence spermatogenesis in rats. These modifications also influence normal function and organization of spermatogenic cells, and after induction of diabetes, modification of germinal epithelial cells of seminiferous tubules populations arise [63]. One investigation noted that the co-administration of Metformin and honey could prevent damages induced by diabetes in testicular tissue, simultaneous administration of metformin and honey could fairly up-regulate diabetes-induced decreased levels of insulin, LH, FSH and testosterone and could increase endocrine activities of the testes, partly by regulating levels of gonadotropins. [64].

### **Metformin impact on sperm quality**

There has been current controversy regarding modifications in sperm counts. World widely, it has been stated that in the last two decades that sperm count is decreasing compared with the last 60 years [65].

There is now a provided proof that male obesity negatively influences male fertility potential not only sperm quality decrease, but also, especially, modifying testicular- germ cell physical and molecular structure and in the long run influence mature sperm. Current data has confirmed that obesity in men impairs children's metabolic and reproductive health. These recommend that paternal health cues are inherited to the next generation with the mediator happening via the sperm most likely. O note is that, the molecular profile of testicular germ cell and sperm from obese adult males is modified with alterations to epigenetic modifiers [66], metformin therapy and improved diet could increase sperm quality, sperm motility, sperm concentration and promote the antioxidant capacity of the testis in obese rats [67].

Another study said that metformin harms somebody organs like the testis. In which, it increases the lipid peroxidation levels and reduces the epididymal sperm count and motility and testicular superoxide dismutase, glutathione, Catalase, and serum aspartate aminotransferase (AST), as well as conjugated bilirubin, were markedly influenced. Also, marked necrosis, degeneration of seminiferous tubules, and defoliation of spermatocytes in the testis are observed [68].

Numerous investigations revealed that diabetes is associated with the high stage of oxidative DNA damage and with the elevated susceptibility to mutagens and the reduced effectiveness of DNA repair [69]; metformin significantly reduced genomic variability and cell proliferation modifications induced by diabetes in somatic and germinal cells in a dose-dependent manner (2500, 500, >100 mg/kg); metformin may protect from genomic instability caused by hyperglycemia, reduce the oxidative stress, and protect from sperm malformation as it is a non-genotoxic or cytotoxic compound [70].

The administration of metformin plus pioglitazone meaningfully enhanced the P/N ratio (polychromatic: normochromatic erythrocytes), decreased the number of micronucleated erythrocytes, decreased the sperm morphology defects and enhanced the caudal sperm count compared with the untreated diabetic condition. Moreso, the metformin and pioglitazone combination promoted the antioxidant status in diabetic animals [71].

In another study, results show that there is an insignificant variation concerning semen volume, liquefaction time, pH, and normal morphology at baseline and after three months of treatment with metformin 850 mg two times per day, but there is a significant difference regarding sperm count and sperm activity at the baseline (before treatment) and after three months of treatment with metformin and decrease in LH, FSH, prolactin, estradiol, and testosterone [72].

#### **Effect of Metformin on Erectile Dysfunction (ED)**

The total frequency of erectile dysfunction (ED) in men in their 2nd decade was 18.4%; The results revealed that erectile dysfunction influences 18 million men in the United States. The frequency of erectile dysfunction was associated with age in a highly positive manner, but it is primarily common among men with one or more risk factors like hypertension, and a history of cardiovascular illnesses, even after drop age consideration. Among diabetic men, the prevalence of erectile dysfunction was 51.3%. Multivariable analyses showed that erectile dysfunction was independently correlated with lower education, diabetes, and lack of exercise [73].

Erectile dysfunction may result from psychological, neurological, hormonal, arterial, or cavernosal impairment or a combination of these factors like drug-induced and systemic disease or aging-related factors [74].

There have been numerous groupings that were proposed for Erectile Dysfunction. Some are on the basis of the cause (iatrogenic, diabetic, and traumatic), and others are on the basis of the neurovascular mechanism of the erectile process like failure to start (neurogenic), failure to fill (arterial), and failure to store (venous). Arteriogenic Erectly Dysfunction can occur through three major mechanisms have (I) impairment of Endothelium-dependent vasodilatation which is mediated by reduced bioavailability of nitric oxide (NO); (II) elevation of Sympathetic nerve activity, resulting in enhancement of basal and myogenic tone within the corpus cavernosum, (III) atherosclerotic luminal narrowing, leading to decreased penile in-flow [75].

In males, insulin resistance has been found to triggers endothelial dysfunction and this contributes to erectile dysfunction and cardiovascular disease [76].

Insulin resistance is considered as the main risk factor for ED, in a state of insulin resistance, basal levels of serum insulin are increased. This rise of insulin complicates the erectile function process which is mentioned above by the following mechanisms: (I) decreasing nitric oxide bioavailability and inducing vasoconstriction; (II) improving the sympathetic nervous system activity; (III) promoting atherogenic risk factors such as hypertension. Furthermore, chronic hypertension nurtures an environment for inflammation, oxidative stress, and endothelial injury, result in further impairment in the dilation of arteries, arterioles, and sinusoids of the corpus cavernosum; Consequently, metformin may be beneficial to address erectly dysfunction, normally attributed to impaired endothelial-dependent vasodilation [77].

Although, Rey-Valzacchi et al. (2012) assumed that improving metabolic profile leads to a beneficial influence on cavernosal NO signaling. The vascular modification by metformin was induced irrespective of whether there is significant glycemic control influence by metformin in streptozotocin-diabetic rats or not. This proposes that metformin has a primary and secondary influence on vessels [78].

Labazi et al. (2013), produced a model of erect dysfunction in a rat model utilizing angiotensin II, which results in contraction of the corpus cavernosum. Metformin 500 mg/kg/day reverse ED induced by angiotensin II and

normal intracavernosal muscle tone had been achieved as well as enhanced endothelial nitric oxide synthase phosphorylation [79].

Moreover, metformin had attenuated the reactions of the sympathetic nervous system, especially of those alpha-1 adrenoceptors which are activated by norepinephrine and restoring corpus cavernosum erectile response [77]. In an investigation, the influence of treatment with metformin on the response to sildenafil in patients with erectile dysfunction and insulin resistance was assessed in a prospective, randomized, controlled, double-blind placebo research. It noted that after treating with metformin, patients with erectile dysfunction experienced a notable enhancement in the international index of erectile function score and a significant reduction in homeostatic model assessment for insulin resistance (HOMA-IR) score [80].

## CONCLUSION

Metformin is an oral anti-diabetic agent with anti-hyperglycemic activity considered as the first line of treatment of non-insulin-dependent diabetes mellitus, as it is a well-tolerated, reasonable price; it is used by over 100 million diabetes patient over the world. Recently, it has been reported that this drug can act in different organs and tissues including the male reproductive system. However, the existing literature presents some contradictory findings on the influence of metformin on this system. While several studies provide evidence that metformin improves sperm motility, sperm count, sperm concentration, and antioxidant status and decreases oxidative stress, some studies didn't prove that according to the impact of other factors, which will lead us to do further studies.

## Conflict of interest

The authors declared that there was no conflict of interest.

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