

## Causes of Infertility in Men with Diabetes

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### Abstract

Diabetes mellitus (DM) is a serious chronic disease that can lead to various complications due to prolonged hyperglycemia. Complications in diabetes are associated with changes that occur in blood vessels and nerve fibers.

Sexual function is one of the key elements of a man's normal lifestyle. Diabetes can affect a man's reproductive function and lead to infertility. This may be due to the deterioration of sperm quality and decrease in its quantity, as well as a violation of stethoscope function. In men, sexual dysfunction includes disorders: erection, ejaculation, libido and orgasm.

**Object:** reduced fertility as a result of diabetes.

**Research methods:** a review of literary sources.

**Results:** There are quite several reasons for infertility and reduced fertility in men with DM, including complications of DM (erectile dysfunction, retrograde ejaculation), hormonal disorders (hypogonadism, obesity, hypothyroidism), psychogenic factors (depressive and affective disorders, syndromes of irritability and phobias), sexually transmitted infections. Certain groups of medications, including psychotropics, antiarrhythmics, hypotensive drugs, and antiandrogens, can affect a decrease in libido and erections. At the same time, taking certain antidiabetic drugs, such as metformin and pioglitazone, can improve sperm quality and thus fertility in men with diabetes. Vitamin E can also be attributed to drugs with a protective effect on male fertility; taking this micronutrient, according to the literature, can improve the state of spermatogenesis in men with diabetes and oligospermia.

**Conclusions:** The issue of male infertility concerns not only the demographic situation, but also men's health in general: both physical and mental. Considering the above, it is worth saying that the diagnosis and successful treatment of infertility in men with DM requires a multidisciplinary team of doctors, such a modern format allows analyzing the problem from different angles and increases the effectiveness of medical care, especially in comorbid patients.

**Keywords:** diabetes in men; erectile dysfunction; retrograde ejaculation; hypogonadism; obesity; infertility; metformin

### Introduction

Diabetes mellitus (DM) is considered one of the most common chronic diseases, as well as endocrine and metabolic disorders that threaten global health. Today, diabetes is the fifth cause of death in Western societies, as well as the fourth most common reason for consulting a doctor [14]. Accordingly, DM and related diseases in men can affect reproductive function and lead to reduced fertility due to erectile dysfunction (ED), decreased sex drive, orgasmic disorder, retrograde ejaculation, and other disorders. The pathophysiology of ED and other disorders of the reproductive system in DM is multifactorial and includes vascular, hormonal, and neurological complications. Considering the above, the topic is relevant and interesting for doctors of various specialties. Also, the authors aimed to reveal the topic of possible prevention of infertility in men with diabetes.

### Analysis of literary data

#### Erectile dysfunction in patients with diabetes

The most common form of sexual dysfunction in men is erectile dysfunction (ED). DM is characterized by its chronic, progressive nature and negative impact not only on the course of DM but also on reduced fertility [22]. Unfortunately, the exact prevalence rates of ED, orgasm disorders, and ejaculation problems are not precisely determined. ED occurs in a significant number of men with DM, and its frequency is estimated to be very high, ranging from 20 to 71% according to various studies [14].

According to the Massachusetts Male Aging Study (MMAS), the prevalence of ED was 52% among men aged 40-69 years (mean follow-up: 8.8 years) [11]. According to the data of this study, the most frequent causes of organic ED are arterial hypertension (AG), type 2 diabetes mellitus, and cardiovascular diseases.

According to the literature, there is a close relationship between the prevalence and growth rates of ED with age. According to literature data, ED is diagnosed in 35–75% of men with type 2 diabetes. There is a correlation between the severity of ED and the duration of diabetes, glycemic control, and the presence of chronic complications of diabetes [11, 22, 38].

Urologists call erectile function the "portal of men's health" because there is a relationship between sexual dysfunction and certain diseases. According to the literature, there is a correspondence between the causes of ED and cardiovascular pathology. Therefore, ED can be a warning signal for early intervention – adequate and aggressive treatment in men of any risk factors. In men without DM, erectile dysfunction can be considered a possible predictor of the development of DM-2 and a marker of the progression of vascular complications of DM [11,29].

### **Violations of sexual function in patients with diabetes**

Endothelial dysfunction of sinusoidal cells is the cause of a decrease in nitric oxide and impaired vasodilation [11].

With diabetes, hyperglycemia causes glycation of elastic fibers, which can be the cause of insufficient relaxation of the cavernous bodies of the penis during

erection. Diabetic polyneuropathy is found in more than 50% of patients with diabetes mellitus, its consequence can be a lack of neuronal transmission from the spinal cord, which also worsens the sexual function of men. At the same time, with diabetes, there is a violation of not only carbohydrate but also lipid metabolism, as a result of which atherosclerotic changes develop in penile arteries [11]. Also, an important mechanism of the development of ED in diabetes is a decrease in the production of neuronal NO-synthase and, as a result, a decrease in the release of NO by the smooth muscles of the cavernous bodies of the penis [5, 6, 33].

### **Violation of ejaculation in diabetes**

Retrograde ejaculation is a pathological movement of sperm at the end of sexual intercourse, as a result of which sperm enters the bladder instead of exiting. There is a distinction between partial and complete retrograde ejaculation. Retrograde ejaculation is often perceived by the patient as the absence of ejaculation with a preserved orgasm. This ejaculation is not dangerous for health, because the sperm combines with urine and is excreted during urination. However, complete retrograde ejaculation is one of the causes of male infertility. According to the literature, retrograde ejaculation occurs only in type 1 diabetes in men with diabetes [10,18]. (Table 1).

**Table 1:** Distribution of sexual dysfunction in patients with diabetes

Violation of sexual function	Patients with type 1 diabetes, %	Patients with type 2 diabetes, %
Erectile dysfunction		
Weak erection	33	53
Complete erectile failure	20	20
Violation of ejaculation		
Detained	6,6	13,3
Retrograde	13,3	-
Premature	12	15
Decreased libido	7	30
Decreased orgasm	20	35

Retrograde ejaculation belongs to the urogenital form of diabetic autonomic neuropathy; disruption of the parasympathetic component of the autonomic nervous system affects erectile dysfunction, while disruption of the sympathetic component leads to insufficient ejaculation and retrograde ejaculation.

### **Hypogonadism and obesity in men with diabetes**

In addition to the mechanisms just mentioned, men with type 2 diabetes have androgen

deficiency - hypogonadism, which can lead to both erectile dysfunction and decreased sex drive and as a result - decreased fertility. According to the literature, 32–35% of men with ED and DM have decreased testosterone. The main reasons are a decrease in the level of androgens with age and obesity. In obesity, leptin stimulates gonadotropic releasing hormone. Constant hyperstimulation eventually causes a decrease in the number and sensitivity of gonadotropin-releasing hormone receptors, which reduces the level of production of this hormone by the pituitary gland. With obesity in men, there is an

excess of estrogens, which are formed in adipose tissue from androgens of adrenal and testicular origin [4, 5, 6, 21, 23, 28, 33, 35-37].

### Other causes of reduced fertility in men with diabetes

In men with DM, in addition to organic causes of erectile dysfunction, there are also psychogenic factors, which include depressive and affective disorders, obsessive-compulsive syndromes and phobias, which are observed in 15-20% of men with DM [10]. In continuation of the topic about the causes of reduced fertility in men, we should mention sexual infections, which, according to the literature, account for 11-15% of cases of the so-called male infertility factor [16]. In addition to hormonal disorders and diabetic polyneuropathy, the cause of erectile dysfunction in men with diabetes can be the use of drugs that can lead to erectile dysfunction. Drugs associated with erectile dysfunction include the following groups: antiarrhythmics, antiandrogens, hypotensive and psychotropic drugs [11, 14, 15, 27, 30, 32]. The positive effect of the first classes of hypoglycemic drugs, amino acids and vitamins on the fertility of men with diabetes. In the literature, there are quite a few articles devoted to the study of the effect of drugs on the fertility of men with diabetes. We bring to your attention a description of several interesting clinical studies in which the influence of medications on sperm quality in men with diabetes was studied. A study published in the same journal in 2020 looked at the effects of pioglitazone on sperm quality and urination in patients with type 2 diabetes. Patients were divided into two groups: those who received pioglitazone and those who received a placebo. The study found that the pioglitazone group had improved sperm quality and a lower risk of erectile dysfunction compared to the placebo group [20].

A study by Lee, J. H., Kim, J. Y., Lee, J. Y., Moon, D. G., & Lee, H. S. (2020) published in the World Journal of Men's Health examined the effects of pioglitazone on sperm quality and urination in patients with type 2 diabetes type the study involved 56 men with type 2 diabetes who had problems with sperm quality and urination. Participants were divided into two groups: a pioglitazone group and a control group. A study found that pioglitazone improved sperm quality and urination in patients with type 2 diabetes. In the pioglitazone group, the improvement was due to a reduction in inflammation and oxidative stress in the body, which had a positive

effect on the function of the genital organs. Therefore, the study showed that pioglitazone may be an effective drug to improve sperm quality and urination in patients with type 2 diabetes. A study published in the Journal of Diabetes Investigation in 2020 examined the effects of metformin on sperm quality and sperm DNA fragmentation in men with type 2 diabetes and oligoasthenozoospermia. 50 men with type 2 diabetes and sperm quality disorders participated in the study. Participants were divided into two groups: a metformin group and a control group. A study found that taking metformin in patients with type 2 diabetes improved sperm quality and reduced sperm DNA fragmentation. However, improvement occurs only in patients with minor sperm quality disorders, and in those with more severe sperm quality disorders, metformin did not show efficacy [39]. Therefore, the study showed that metformin may be an effective drug to improve sperm quality and reduce sperm DNA fragmentation in type 2 DM patients with mild sperm quality abnormalities. The results of another randomized clinical trial examining the effect of metformin on fertility in men with diabetes were published in the journal *Andrologia* in 2019. The study included 60 men with idiopathic oligoasthenoteratozoospermia and pre-existing diabetes who received metformin (1500 mg daily) for 3 months. The results showed an improvement in sperm concentration and motility in men treated with metformin. In addition, they had improvements in ejaculate parameters such as volume and pH [12]. These results indicate a potential benefit of metformin in improving sperm parameters in men with oligoasthenoteratozoospermia and pre-existing DM. However, further studies are needed to confirm these results and establish the optimal dose of metformin.

A study published in the International Journal of Impotence Research in 2020 examined the effects of exposure to L-arginine and PDE5 inhibitors on sperm quality in men with diabetes and erectile dysfunction. 80 men diagnosed with diabetes and infertility participated in the study. Participants were divided into 4 groups: placebo, L-arginine, sildenafil, and a combination of L-arginine and sildenafil. The study showed that the combination of L-arginine and sildenafil improved sperm quality indicators such as concentration, motility and morphology. [9].

The study of the effect of vitamin E on sperm parameters in men with type 2 diabetes with oligospermia was conducted in a randomized clinical trial published in *Clinical Nutrition ESPEN*. Patients

received vitamin E (400 IU/day) for 3 months, after which sperm quality was assessed. It was found that after 3 months of vitamin E intake, sperm concentration and morphology improved in men with diabetes and oligospermia. In particular, an increase in the number of spermatozoa in the ejaculate, a decrease in the percentage of abnormally formed spermatozoa, and an improvement in their mobility were found. At the same time, the effect was less pronounced in patients with more severe forms of oligospermia. Therefore, the results of the study indicate the possibility of using vitamin E as a means to improve the state of spermatogenesis in men with diabetes and oligospermia. However, it should be noted that the study was conducted on a limited group of patients, so further studies on a larger number of patients are needed to confirm these results [25].

### Treatment of men with diabetes and reduced fertility

Treatment of male infertility in patients with diabetes mellitus depends on the cause of infertility and may include the following approaches:

- treatment of the main disease: maintenance of a normal level of glucose in the blood and control of other concomitant diseases that may affect the state of the reproductive system;
- weight control and prevention of obesity (diet, physical activity);
- lifestyle changes: reducing alcohol consumption, quitting smoking, eating healthy, and exercising can improve sperm quality, improve reproductive function, and prevent obesity, which also adjusts men's hormonal balance;
- use of urological and andrological medicines;
- surgery: in some cases, surgery may be necessary to correct problems with the genitals;
- assisted reproductive technologies: in severe cases, when other treatments fail, assisted reproduction techniques such as ICSI (intracytoplasmic sperm injection) or IVF (in vitro fertilization) may be used;

ICSI (intracytoplasmic sperm injection) is a method of artificial insemination, which is used to treat male infertility associated with the complexity of the process of penetration of the sperm into the egg cell. During the ICSI procedure, one sperm is injected directly into the cytoplasm of the egg for fertilization. This is different from the ICSI procedure, where the sperm moves freely towards the egg, which requires the activity and motility of the sperm. ICSI is usually

used when standard ICSI and IUI (intrauterine insemination) procedures have failed.

Although ICSI is a fairly effective method of treating male infertility, it is not a guarantee of pregnancy. Its effectiveness may depend on many factors, such as the age of the woman, the condition of her ovaries, the quality of the man's sperm, and other medical factors [3,8,24,27,40].

### Prevention of infertility in men with diabetes

According to the authors, the main goal of prevention of steatosis in men with diabetes should be the normalization of the blood glucose level, to prevent the development of diabetes complications, which include diabetic polyneuropathy. According to the recommendations of the American Diabetes Association (ADA), the target values of glycemia are individual, however, the recommended level of glycated hemoglobin in patients with diabetes mellitus is < 7%; this level can be accepted if it can be achieved safely without hypoglycemia or other adverse effects of treatment. Also, the ADA recommendations state that weight control is considered an influential component of sugar-lowering treatment for type 2 diabetes [Standards of Medical Care in Diabetes-2023; Diabetes Care, December 2022, Vol.46, Supplement 1]. Given the negative impact of obesity on the reproductive health of men with diabetes, an important component of prevention is maintaining normal body weight, regular physical activity and a healthy diet, a sharp reduction in alcohol consumption, and smoking cessation. Sexually transmitted infections are an equally important factor in male infertility, so preventive measures include reliable contraception and treatment of chronic urological diseases.

Psychological aspects of fertility disorders are becoming increasingly relevant these days, taking into account the chronic stress state of our men - military operations. Therefore, psychological support and, if necessary, psychotherapeutic support of patients are important preventive measures for sexual function disorders of psychogenic etiology. In addition to organic and psychological reasons, doctors should be aware of the effect of drugs on male fertility, and correct the therapy of concomitant diseases to prevent the negative impact of certain drugs on the reproductive health of men with diabetes.

### Rational nutrition in diabetes and impaired reproductive function

Rational nutrition is the basis of the successful treatment of chronic diseases, and diseases of the

reproductive system are no exception. If we describe the recommendations for men's health in general, then the food should be low-glycemic, with a decrease in the amount of easily digestible carbohydrates (flour products, sweets, etc.), with a sufficient amount of easily digestible protein, on average 80 grams per day (protein is found in eggs, mature cheese, fish, lean meat), fiber (found in bran, vegetables, non-sweet fruits), fermented milk products (kefir, yoghurt without fillers, fermented milk cheese). It is recommended to minimize, and it is better to eliminate, alcohol. Sharply reduce, or better yet eliminate, processed meat products (sausage, sausages, various smoked meats) from the diet, because these products contain genetically modified soy, excess salt, and phytoestrogens. Regular physical activity and self-monitoring of weight and vital indicators are necessary: arterial pressure, pulse, glycemia, etc [17].

## Conclusions

The issue of male infertility concerns not only the demographic situation, but also men's health in general: both physical and mental. There are many reasons for infertility and reduced fertility in men with diabetes, they include complications of diabetes (erectile dysfunction, retrograde ejaculation), hormonal disorders (hypogonadism, obesity, hypothyroidism), psychogenic factors (depressive and affective disorders, obsessive-compulsive and phobia syndromes), sexually transmitted infections. Certain groups of medications, including psychotropics, antiarrhythmics, hypotensive drugs, and antiandrogens, can affect a decrease in libido and erections. At the same time, taking certain antidiabetic drugs, such as metformin and pioglitazone, can improve sperm quality and thus fertility in men with diabetes. Vitamin E can also be attributed to drugs with a protective effect on male fertility; taking this micronutrient, according to the literature, can improve the state of spermatogenesis in men with diabetes and oligospermia.

The good news is that many reproductive disorders in men with diabetes can be avoided with proper glycemic control, lifestyle modifications, and a healthy diet. Considering the above, it is worth saying that the diagnosis and successful treatment of infertility in men with DM requires a multidisciplinary team of doctors, such a modern format allows analyzing the problem from different angles and increases the effectiveness of medical care, especially in comorbid patients. Finally, I would like to add that we live in

difficult times: the recent pandemic caused by COVID-19, military operations and the stresses associated with them. So, one of the probable reasons for the decline in male fertility is the chronic stress factor - war. The topic of the impact of the war on the mental and physical health of Ukrainian men is very relevant and requires a separate discussion in the following articles.

## Conflict of interest

The authors declare that there is no conflict of interest and their financial interest in the preparation of this article.

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