



# Male-specific consequences of obesity — functional hypogonadism and fertility disorders

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## Abstract

Obesity is currently one of the most serious public health problems which affects up to 30-40% of the population, and its prevalence is higher in men than in women. Complications of obesity include atherosclerosis, cardiovascular diseases, and type 2 diabetes mellitus, but it also has a negative impact on the hormonal system and fertility. The hormonal consequences of excess body fat in men are functional hypogonadism, which not only causes clinical symptoms of testosterone deficiency, but is also a risk factor for obesity (a vicious circle mechanism). Reduced fertility in obese men may be a consequence of functional hypogonadotropic hypogonadism (decreased gonadotropins and testosterone secretion, reduced libido, and erectile dysfunction), but other mechanisms associated with excess adipose tissue, like hyperinsulinaemia, hyperleptinaemia, chronic inflammation, and oxidative stress also play an important role. Therefore, in obese men deterioration of semen parameters (sperm concentration, motility, and morphology) and reduced fertility are observed, also concerning the effectiveness of assisted reproductive techniques. Reducing the mass of adipose tissue causes an increase in testosterone concentrations and has a beneficial effect on semen parameters. Functional hypogonadism in obese men should be diagnosed only after exclusion of organic causes of hypogonadism. Lifestyle changes, including physical exercise and low-caloric diet, and optimization of comorbidities, are still first line of treatment. In some patients, if such treatment is ineffective, pharmacotherapy or bariatric surgery may be considered. Testosterone replacement therapy is contraindicated in obese men with functional hypogonadism, especially in those who desire fertility. Selective oestrogen receptor modulators and aromatase inhibitors improve sperm quality but are not recommended for the treatment of hypogonadism in obese men. GLP-1 analogues appear to be effective and safe in the treatment of low testosterone and infertility in obese men and may be the main method of pharmacotherapy in the future.

**Key words:** obesity; men; hypogonadism; infertility; bariatric surgery; testosterone replacement therapy; GLP-1 analogues

## Introduction

According to the World Health Organization (WHO), in 2018 about 39% of adults were overweight and 13% were obese, which means that an estimated 1.4 billion people are currently considered as overweight or obese, including over 200 million obese males, and this is expected to increase to more than 40% of the global population by 2030 [1]. The data obtained by the National Institute of Public Health in Poland reported in 2020 that overweight was observed in 64% and obesity in 12% of men, while among men aged 20–44 years the prevalence of both was almost 2 times higher in men than in women [2].

These epidemiological data indicate that overweight and obesity are an increasingly common health problem in men of all ages, especially in reproductive age, and can cause endocrine disorders, negatively affect reproductive capacity, and are a risk factor for associated comorbidities. The most important complication of obesity in men is an increased risk of type 2 diabetes, atherosclerosis, and cancer, which lead to increased mortality. Unfortunately, the diagnosis and treatment of obesity

are difficult because it results from complex interactions between hormonal, genetic, nutritional, environmental, metabolic, and psychosocial factors.

Obesity is also associated with gonadal dysfunction. In women, obesity is associated with a risk of polycystic ovary syndrome (PCOS), while in men it causes the so-called male obesity-associated secondary hypogonadism (MOSH), more commonly called functional hypogonadism (FH). These functional disorders of the male gonads cause clinical symptoms of hypogonadism, such as erectile dysfunction, decreased libido, depressed mood, and metabolic complications, but they are also a significant and increasingly frequent cause of fertility disorders in men. Unfortunately, functional hypogonadism is also the cause of the aggravation of obesity, so we observe the classic mechanism of a vicious circle.

Since about 50% of the causes of fertility disorders in a couple are male factors, it seems that obesity and its consequences may play an extremely important role in the pathogenesis of infertility in men. Thus, understanding the causes and management of obesity in men has become an important problem of public health.



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## Pathogenesis of functional hypogonadism in obese men

Functional hypogonadism (also referred to as adult-onset hypogonadism) is defined as “the coexistence of androgen deficiency-like features and low serum testosterone (T) concentrations occurring in the absence of both intrinsic structural hypothalamic-pituitary-testis (HPT) axis pathology and of specific pathologic conditions suppressing the HPT axis (such as microprolactinoma, endogenous Cushing syndrome) in middle-aged or older men” [3]. The European Male Aging Study revealed that T levels decline with age, comorbidities (e.g. obesity) may further reduce T concentration, and the prevalence of FH in middle-aged and older men varies from 2.1% to 12.3% [4]. The characteristic feature, which distinguishes FH from other types of hypogonadism (primary or secondary), is its potential reversibility if the underlying causes are removed or treated. There is a consensus that the most important cause of FH is obesity, which is why the term MOSH was proposed [5], but in practice it is unlikely that obesity is the sole cause of FH. Therefore, the term FH is used more often, which considers other causes of T deficiency such as advancing age, stress, excessive sport, and comorbidities.

Obesity-associated FH has been intensively studied for several years, during which time it has been shown that men with a BMI of 35–40 kg/m<sup>2</sup> can have up to 50% less free and total T when compared to age-matched peers with body mass index (BMI) < 25 kg/m<sup>2</sup> [6], and an 8.7-fold increase in risk of hypogonadism in men with a BMI > 30 kg/m<sup>2</sup> has been demonstrated [4].

In 1999, Cohen et al. suggested that obesity is a risk factor for T deficiency, but hypogonadism promotes obesity, leading to a vicious cycle, and the most effective way to increase T levels is to reduce body fat mass [7]. A classic example of this bidirectional relationship is the rapid weight gain observed in patients with prostate cancer undergoing androgen deprivation therapy [8], while reducing body fat through bariatric surgery or pharmacologically with liraglutide increases T levels [9–11].

There is currently no doubt that obesity causes hypogonadism (and vice versa), but the exact pathophysiological mechanisms remain to be elucidated; however, it is emphasized that they are complex and multifactorial.

### *Aromatisation of testosterone to estradiol in fat tissue*

In men with obesity the expression of aromatase enzyme (CYP19A1) in the adipocytes is increased, which enhances the conversion of T to estradiol (E2).

This conversion leads to a decrease in serum total T and further fat deposition (adipocyte hypertrophy), while an increase in E2 has a suppressive effect on hypothalamo-pituitary function (negative feedback), and in patients with FH luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are reduced or inadequately normal in relation to low T concentrations. These observations point to a hypothalamic defect, especially since the gonadotropin response to gonadotropin-releasing hormone (GnRH) stimulation is normal [7].

In addition to the inhibitory effect of elevated E2 on the HPT axis, E2 also stimulates the hepatic synthesis of sex hormone binding globulin (SHBG). In the circulation, 98% of T is bound to albumin (40%) and SHBG (about 58%), and only 1–2% of it is free T, which acts on tissue androgen receptors [12]. Therefore, in men with hyperoestrogenism as a result of obesity, a decrease in free T levels and clinical signs of hypogonadism are observed.

### *SHBG and obesity*

In obese men, the mechanism described above is partially compensated because low SHBG levels are present in obese men. It was previously thought that low SHBG concentrations were only the result of insulin resistance (hyperinsulinaemia), but they seem to be related rather to the high pro-inflammatory cytokines interleukin 1 (IL-1) and tumour necrosis factor alpha (TNF- $\alpha$ ), and to high lipid content of the liver [13]. Until recently, it was thought that SHBG was only a “storehouse” for T, but now it is emphasized that SHBG exerts a direct anti-inflammatory effect and additionally reduces fat content in adipose tissue cells (adipocytes) as well as in macrophages [14].

### *Insulin resistance and obesity*

In obese men with hypogonadism multipotential mesenchymal cells of fat tissues are preferentially differentiate to adipocytes instead to myocytes, causing unfavourable changes in body composition (visceral obesity and sarcopenia) and insulin resistance. This phenomenon results in increasing of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1, and IL-6) and decreasing adiponectin [14, 15]. Hyperinsulinaemia in obese men also inhibits hypothalamic kisspeptin-dependent signalling and reduces pulsatile GnRH secretion, leading to functional hypogonadotropic hypogonadism as well as to peripheral hypogonadism through direct actions on Leydig cells [15].

However, insulin resistance and SHBG are independently correlated with low free T levels in obese males. The impact of insulin resistance and SHBG on T levels in the population of obese men was investigated [17].

T deficiency was present in 52.0% of the enrolled patients, but this percentage dropped to 17.6% when only free T was accounted for, because SHBG levels were correlated negatively with BMI. The authors observed that higher homeostasis model assessment of insulin resistance (HOMA-IR) and lower SHBG levels were independently correlated with lower free T. They concluded that insulin resistance seems to be the main determinant of low T levels in obese males; however, low SHBG levels were correlated with low free T even after HOMA-IR adjustment. This suggests that SHBG can be associated with T deficiency beyond the influence of insulin resistance.

Insulin resistance, and low SHBG and T form a specific “triad” that significantly contributes to the diabetic and prediabetic state in men. In the Massachusetts Male Aging Study (MMAS) the authors observed in 1156 patients over 7–10 years that low levels of T and SHBG were strongly associated with the development of diabetes in men. Also, the incidence of FH was investigated in the population of Polish obese, diabetic men [19]. We observed that diabetic men had statistically higher E2 concentration than non-obese control men, 46% of diabetic men were hypogonadal, and 93% of them had functional hypogonadotropic hypogonadism. BMI and total T as well as free T concentrations showed a statistically significant inverse relationship ( $r = -0.362$ ), and there was an inverse relationship between BMI and calculated free T levels.

#### ***Leptin resistance, kisspeptin, and obesity***

Another important player in the pathophysiology of FH in obese men is leptin produced by adipocytes, which acts to regulate energy balance ensuring reduced fat storage. The physiological role of leptin is to stimulate kisspeptin neurons, which in turn stimulates hypothalamic neurons to secrete GnRH and consequently LH in the pituitary, while T inhibits the secretion of leptin in adipocytes and regulates physiological T-leptin-kisspeptin-GnRH feedback [20]. However, obesity in men causes an increase in leptin secretion in adipocytes and consequently a central leptin resistance at the hypothalamo-pituitary level. Similarly to hyperinsulinism, leptin not only inhibits the secretion of GnRH and LH but also reduces the sensitivity of Leydig cells to LH [20–21]. Thus, hyperinsulinism and leptin resistance, in similar mechanisms, play a role in the pathomechanism of FH in obese men.

#### ***Proinflammatory cytokines and obesity***

The last important players in the pathophysiology of FH in obese men are proinflammatory cytokines. As mentioned, T deficiency promotes the formation of adipocytes from pluripotent mesenchymal cells,

while T action exerts an anti-inflammatory effect on fat tissue (decreasing leptin, TNF- $\alpha$ , IL-6, osteopontin, and monocyte chemoattractant protein-1 $\alpha$ , and increasing adiponectin and visfatin) because it prevents adipocyte hypertrophy. Additionally, T improves insulin sensitivity and reduces CRP secretion from the liver [14, 22].

The consequence of tissue hyperplasia in obese men, partially related to FH, is not only increased E2, leptin, and insulin resistance, but also synthesis of pro-inflammatory adipokines (proinflammatory state) like IL-1, IL-6, and TNF- $\alpha$ , which are secreted from adipocytes and strongly activate macrophages, as well as decreased secretion of adiponectin [22]. Elevated concentrations of pro-inflammatory cytokines intensify the general inflammation state and worsen the sensitivity of tissues to insulin and are an additional factor impairing kisspeptin signalling in the hypothalamus and inhibiting GnRH secretion [20, 23].

#### ***Summary model of GnRH secretion regulation in obese men***

The key element directly regulating GnRH secretion is kisspeptin, the neurons of which are located in the infundibular nucleus. The role of kisspeptin is to stimulate GnRH neurons through specific receptors (KISS1R) in the preoptic area of the hypothalamus and consequently the secretion of LH, FSH, and T, and it indirectly affects spermatogenesis. Because kisspeptin neurons have receptors for insulin, leptin, and E2, leptin resistance as well as hyperinsulinism and hyperoestrogenism cause disorders of the kisspeptin-GnRH axis and, consequently, a decrease in T synthesis in Leydig cells. Pro-inflammatory cytokines present similar adverse effects on GnRH secretion. In addition, a direct inhibitory effect of hyperinsulinism and leptin resistance on Leydig cells participate in the pathomechanism of FH and fertility disorders in obese men [14, 24]. These disorders are referred to as FH, but from the endocrinologist's point of view, it is hypogonadotropic hypogonadism, i.e. secondary. Factors that may cause FH in obese men are summarized in Table 1.

#### ***Testosterone levels in obese men***

Several cross-sectional observational studies reported lower T levels in men with obesity, diabetes, or metabolic syndrome as compared to control subjects [25–26], but not all studies have shown such a relationship. Data from the MMAS demonstrated that middle-aged men who became overweight during many years of follow-up presented lower total T and SHBG, but not free T levels [27]. It should be remembered that only free T, and to a lesser extent

**Table 1.** Factors that may cause functional hypogonadism (FH) in obese men.

Factor	Central mechanism	Peripheral mechanism
Estradiol excess	GnRH secretion inhibition	Increase in SHBG
Insulin resistance	GnRH secretion inhibition	Leydig cell inhibition
Leptin resistance	GnRH secretion inhibition	Leydig cell inhibition
Pro-inflammatory cytokines	GnRH secretion inhibition	Insulin resistance

GnRH — gonadoliberein; SHBG — sex hormone binding globulin

the albumin-bound testosterone (often referred to as bioavailable T), affects the receptors, so these patients probably did not have clinical signs of hypogonadism. Also, low SHBG concentrations, which are characteristic in obese men, in some studies correlated with subsequent metabolic risk, e.g. obesity [28].

SHBG and free T levels should be considered when diagnosing hormonal disorders in obese men because studies showed more consistent associations between free T (or bioavailable T) and androgen-related outcomes such as sexual desire than with total T levels [29]. Because, as mentioned earlier, in obese men SHBG levels are low, contributing to the low total T levels. Only in men with severe visceral obesity is free T significantly decreased [30]. So, the interpretation of hormonal results and diagnosis of hypogonadism in obese men may be complicated, because not at all obese men with low T are truly hypogonadal, i.e. with signs and symptoms of hypogonadism. It should be considered that a higher prevalence of sexual and erectile dysfunction (ED) and decreased semen quality in men with obesity with or without low total T levels were observed [31]. Importantly, most obese men still have normal free T levels and lack of hypogonadal signs, so they cannot be considered truly hypogonadal.

## Erectile dysfunction, FH, and obesity

Hypogonadism leads to difficulties in achieving and maintaining an erection. Erectile function is dependent on interactions of erectile tissue, and several endocrine and psychological factors. Hypogonadism, often observed in obese men, is one of most important risk factors of ED and one the most specific symptoms of hypogonadism.

In population of 3369 men between the ages of 40 and 79 years at 8 European centres T levels have been correlated with clinical symptoms considered to be specific to hypogonadism. The results of the European Male Aging Study (EMAS) showed that sexual symptoms (poor morning erection, low sexual desire and ED) had a syndromic association with decreased T levels (total T level of less than 11 nmol per litre (3.2 ng/mL) and a free T level of less than 220 pmol per litre (64 pg/mL). Also,

an inverse relationship between an increased number of sexual symptoms and a decreased T level was observed [32].

Previous studies have shown a significant impact of obesity on the risk of ED. In a cross-sectional analysis of data from a prospective cohort study of 31,742 men aged 53 to 90 years, obesity was associated with higher risk of ED: relative risk, 1.3 [confidence interval (CI), 1.2 to 1.4] for body mass index (BMI) > 28.7 kg/m<sup>2</sup> vs. < 23.2 kg/m<sup>2</sup> [33]. In the MMAS, a random-sample cohort study, including 513 men aged 40–70 years, overweight (BMI ≥ 28 kg/m<sup>2</sup>) was found in 79% of subjects with ED [34].

Also, a study performed on a population of Polish men over 65 years old with ED, with or without obesity, showed a relationship between low T and ED. The degree of ED was significantly higher in men with lower T levels (inverse relationship between IIEF-5 score and total T), and obesity was found in 91% of men with T levels < 350 ng/dL [35]. Also, in population of Polish prediabetic men (mean BMI > 29 kg/m<sup>2</sup>), the prevalence of ED in patients with prediabetes was higher than in the control group (30 vs. 24%) and was associated with low free T levels [36].

A recent meta-analysis of the association between BMI and ED in 42,489 men revealed that the prevalence of ED was significantly higher in overweight men [odds ratio (OR) = 1.31; 95% CI: 1.13–1.51; I<sup>2</sup> = 72%] and in men with obesity (OR = 1.60; 95% CI: 1.29–1.98; I<sup>2</sup> = 79%), and ED was associated with significant higher values of BMI (MD = 0.769; 95% CI: 0.565–0.973 kg/m<sup>2</sup>; I<sup>2</sup> = 78%) [37].

Obesity results not only in ED, but also increased difficulty with sexual performance, leading to lower satisfaction with sexual life, reduced libido, and coital frequency.

## Fertility and obesity in men

The HPT axis is the principal endocrine regulator of reproductive functions. As described in detail in the previous chapter, obesity in men is associated with FH, which is characterized by impaired pulsatile GnRH secretion, resulting in decreased LH and FSH synthesis. These



gonadotropins are the key regulatory hormones acting upon the testicular cells. FSH acts upon the Sertoli cells to regulate spermatogenesis indirectly and stimulates synthesis of inhibin by Sertoli cells. Inhibin acts directly through a negative feedback mechanism to downregulate pituitary FSH release, while LH acts on the Leydig cells to upregulate steroidogenesis and T synthesis, which further mediates spermatogenesis by its nuclear receptors in Sertoli cells [38]. In obesity E2 levels are elevated, and because they inhibit GnRH neurons (in feedback mechanism) more strongly than T, hyperoestrogenism leads to subsequent insufficiency of LH and FSH for steroidogenesis and spermatogenesis and induced systemic inflammation negatively influenced on steroidogenesis in testes [39].

The pathomechanism of fertility disorders in obese men is not only due to elevated E2. Excess adipose tissue causes disturbances in the secretion of many other hormones and substances synthesized in this tissue and affecting spermatogenesis.

In obese men, adipokines, such as adiponectin, ghrelin, orexin, leptin, obestatin, and inflammatory cytokines, disrupt normal reproductive hormonal regulation of spermatogenesis [40]. Obesity-related reduction of orexins causes an imbalance of energy homeostasis and consequently reduces fertility, while increased resistin levels reduce insulin sensitivity and play a role in FH and diabetes pathogenesis. Additionally, orexin aggravates cellular oxidative stress, whereas elevated adiponectin levels correlate with low levels of testosterone, as well as ghrelin. Hyperinsulinaemia and leptin resistance may decrease T, which is necessary for normal spermatogenesis [41], but the effect of leptin is more complex. Leptin deficiency in mice has shown impaired spermatogenesis; however, excessive leptin secretion in obese men impairs spermatogenesis, which induces overproduction of reactive oxygen species (ROS) in endothelium [42]. The mechanisms underlying fertility disorders in obese men are very complex and multifactorial.

One of the factors often observed in obese men and affecting spermatogenesis is raised gonadal temperature resulting from increased scrotal adiposity. Optimal scrotal heat for normal spermatogenesis ranges between 34°C and 35°C, while elevated temperatures within the scrotum in obesity may impair spermatogenesis [40]. Increased testicular temperature has a negative effect on all basic semen parameters (sperm motility, morphology), and it increases sperm DNA fragmentation (SDF) and sperm oxidative stress [43].

It has been shown that oxidative stress increases with an increase in BMI, possibly due to excessive seminal macrophage activation resulting in decreased sperm motility and increased SDF. Probably an impor-

tant role in this action is played by ROS stimulated, among others, by high leptin levels and by elevated fatty acid oxidation in mitochondria and peroxisome [44]. The increase in ROS observed in obesity leads to oxidation of polyunsaturated fatty acids in sperm membrane, loss of mitochondrial membrane potential, and single- and double-strand SDF. BMI greater than 25 kg/m<sup>2</sup> is accompanied by increased DNA fragmentation index (DFI) (percentage of spermatozoon with high single- or double-strand breaks in nuclear SDF) [45].

In recent decades we have observed a gradual decrease in semen parameters [46]. Numerous studies have shown that overweight (BMI > 25 kg/m<sup>2</sup>) and obesity in men correlate with worse seminological results, mainly the prevalence of oligozoospermia and azoospermia, reduced ejaculate volume, and decreased sperm motility (asthenozoospermia) and morphology (teratozoospermia). The risk of oligozoospermia (concentration < 15 million/ml) is threefold higher than in normal men [47].

In 2023 the first meta-analysis of the relationship between BMI and sperm count was published [48]. In a sample of 13,077 men from the general population attending fertility clinics, the authors observed a J-shaped relationship between BMI categories and risk of oligozoospermia or azoospermia. Compared with men of normal weight, the odds ratio (95% CI) for oligozoospermia or azoospermia was 1.15 (0.93–1.43) for underweight, 1.11 (1.01–1.21) for overweight, 1.28 (1.06–1.55) for obese, and 2.04 (1.59–2.62) for morbidly obese men; therefore, overweight and obesity were associated with an increased prevalence of azoospermia or oligozoospermia.

Recent meta-analyses have confirmed the adverse effect of obesity on semen parameters and fertility in men. The analysis was based on the qualitative analysis of 60 studies and quantitative analysis of 28 studies (mainly cross-sectional) assessing semen parameters in overweight and obese men aged from 16 to 66 years. Qualitative analysis of the data revealed that overweight or obesity was associated with reduced semen quality parameters (i.e. semen volume, sperm count and concentration, sperm vitality and motility, and normal morphology) and specific hormonal changes (lower inhibin B, total testosterone and sex hormone-binding globulin, higher E2). Quantitative analysis revealed that, compared to individuals with normal weight, those with class I obesity and class II obesity had a lower semen volume, sperm count, a decrease in sperm vitality percentages, and a decrease in spermatozoa with normal morphology [49].

Also, very interesting conclusions are provided by the meta-analysis of associations between obesity and semen quality performed in the general rather than

**Table 2.** Factors that may cause fertility disorders in obese men

Factor	Mechanism	Result
FH, E2 excess, insulin resistance, hyperleptinaemia	GnRH secretion inhibition	Erectile dysfunctions
	Low/inadequate low FSH/LH	Oligozoospermia
Imbalance in adiponectin, ghrelin, orexin, obestatin and inflammatory cytokines levels	Low T	Asthenozoospermia
	ROS overproduction	Teratozoospermia
Raised gonadal temperature	Sperm DNA fragmentation	Low fertilization index
	Oxidative stress	Longer TTP (also ART)

FH — functional hypogonadism; E2 — estradiol; GnRH — gonadoliberein; LH — luteinizing hormone; FSH — folliculotropic hormone; T — testosterone; ROS — reactive oxygen species; TTP — time to pregnancy; ART — assisted reproductive techniques

the infertile population. These analyses showed that obesity had no effect on sperm concentration and percentage of normal sperm morphology, but decreased semen volume, total sperm number, percentage of forward progression, and percentage of viability [50].

When we take into consideration not only semen parameters but fertility (e.g. time to pregnancy — TTP), the influence of obesity on male procreation potential is confirmed and negative. In the Danish National Birth Cohort, BMI and TTP were analysed in 47,835 couples. Among men with a BMI of 18.5 kg/m<sup>2</sup> or more, a dose-response relationship between increasing BMI group and subfecundity (a TTP of more than 12 months) — odds ratio (OR) = 1.19 (95% CI: 1.14–1.24) — for men was found [51].

The influence of male obesity on SDF, fertilization rate, and pregnancy outcome among males attending a fertility clinic for IVF/ICSI treatment was investigated in 750 infertile couples undergoing assisted reproduction technique (ART). The percentage of spermatozoa with chromatin maturity and integrity was reduced in overweight men, and the increase in paternal BMI correlated with the increase in sperm chromatin damage, immaturity, and ROS. Univariant regression analysis revealed that paternal BMI remain predictor of sperm chromatin maturity, successful fertilization, and cumulative live birth rate (CLBR). The authors concluded that paternal overweight should be regarded as one of the predictors for fertilization not only in women but also for men [52]. Factors that may cause fertility disorders in obese men are summarized in Table 2.

## Management of obesity in men

### Lifestyle changes

FH is primarily due to suppression of the HPT axis and is potentially reversible in a significant percentage of patients. The European Academy of Andrology (EAA), in guidelines on investigation, treatment, and monitoring of FH [53], recommends lifestyle changes, including physical exercise and weight reduc-

tion, in overweight and obese men with FH because weight loss may increase T concentrations [53]. Data from EMAS showed that weight loss results in increased T levels in obese men. In 2736 men aged 40–79 years at baseline followed for a mean of  $4.4 \pm 0.3$  years, the authors observed that weight loss greater than 15% was associated with a proportional T increase (2 nmol/L or 58 ng/dL), and weight gain was associated with a proportional T decrease. The rise in testosterone level was proportional to the extent of weight loss achieved [54].

A meta-analysis was published in 2020 regarding the treatment of FH, besides pharmacological substitution [55]. The authors analysed 22 studies evaluating the effect of a low-calorie diet on T levels. These trials enrolled 567 patients with a mean age of 44.9 years, a BMI of 36.0 kg/m<sup>2</sup>, and a mean follow-up of 23 weeks. Meta-analysis showed, that an average diet-induced weight loss of 9.8% was associated with a significant increase in total T of 2.8 nmol/L (1.68–4.07 nmol/L), as well as a significant increase in LH (1.31 mU/L [0.80–1.82 mU/L]) and FSH (1.28–2.30 mU/L), thus the obtained results confirmed earlier data prepared by the same team of authors [56].

Also effects of physical exercise on T levels were analysed [55], and based on the results from 8 trials and 202 enrolled patients with a mean age of 51.8 years, a mean BMI of 28.5 kg/m<sup>2</sup>, and a mean follow-up of 15 weeks, the authors concluded that physical exercise resulted in a significant increase in T levels at the endpoint, and that greater weight loss and longer trial duration are significantly associated with an increase in T levels, independently of age. But the surprise was that for equal weight change, a greater improvement in T levels is observed in older men.

### Bariatric surgery

A meta-analysis of effect of bariatric surgery (BS) on serum levels of sex hormones was published in 2021 [57]. The results revealed that BS caused a significant increase in LH, FSH, total T, and SHBG levels and, con-

versely, decreased dehydroepiandrosterone (DHEA) and E2 levels, in males. The mean increase in T ranged from 8 to 10 nmol/L for T and from 75 to 90 pmol/L for free T. Total E2 was significantly decreased after BS, with a mean reduction of about 20 pmol/L.

Also, the influence of BS on male sexual function was systematically evaluated. [58]. In the analysis a total of 12 studies involving 420 participants were included, and the authors noted that BS causes a significant increase in the International Index of Erectile Function (IIEF) score, erectile function score, sexual desire, sexual intercourse satisfaction, and total satisfaction. However, BS did not affect orgasm function.

Current large meta-analyses on the impact of significant weight reduction (BS) provide ambiguous conclusions. In meta-analyses from 2019 authors evaluated the effects of BS on male sex hormones, sperm parameters, and sexual function. Analysis of 28 cohort studies with 1022 patients enrolled revealed that free T, LH, FSH, and SHBG levels were significantly increased after surgery; however, BS surgery did not affect sperm quality and inhibin B levels [59]. While the meta-analysis from 2022 found that one year after BS sperm parameters, i.e., total sperm count, sperm motility, semen volume, and sperm concentration, except sperm morphology, did not significantly change. Deterioration of sperm morphology (teratozoospermia) in obese men is one of the most common sperm pathologies, and even a small improvement can be beneficial to a couple's fertility. Unfortunately, a recent meta-analysis again failed to confirm the benefits of BS on sperm quality [60]. A total of 9 studies with 218 patients were found and the mean preoperative age distribution of the patients included centralized from 18 to 50 years, and the mean BMI ranged from 36.7 to 70.5 kg/m<sup>2</sup>. The follow-up period ranged from 6 to 24 months. The results revealed that BS had no significant effect on sperm volume, concentration, total count, morphology, total motility, progressive motility, and viability [60]. Therefore, the current data do not allow for an unequivocal assessment of the impact of BS surgery on semen quality, but it seems to have no effect.

#### ***Aromatase inhibitors (AI) and selective oestrogen receptor modulators (SORM)***

SORMs and AIs are drugs that antagonize the effects of E2 at the hypothalamic and pituitary levels. They increase the concentration of LH and FSH, T and have a beneficial effect on spermatogenesis. Their effectiveness in the treatment of infertility in men has been confirmed in the latest meta-analysis. Cumulative results of 10 studies involving 666 patients showed that letrozole or anastrozole administration significantly increased sperm concentration, total sperm count, LH, FSH, and T

levels; however, no effect was shown on sperm motility and morphology [61]. Also, the effectiveness of SORMs (clomiphene) was evaluated in infertile, normogonadotropic patients with idiopathic oligozoospermia. SORM administration significantly increased sperm concentration, total sperm count, sperm morphology, and serum LH, FSH, and T; however, SORMs did not have any significant effect on sperm total motility [62]. It should be clearly noted that both studies analysed patients with idiopathic infertility, without FH (normal LH and FSH), while few of them were obese. Thus, the demonstrated increase in T concentration was not the goal of treatment. Moreover, this increase may not always be beneficial because it may secondarily inhibit FSH secretion.

The effectiveness of SERMs was also analysed in men with obesity and FH. Seven trial studies were analysed, which included 232 patients with obesity-related FH treated with clomiphene (12.5–50 mg daily) or enclomiphene (12.5–25 mg daily) for 1.5–4 months. An increase in T concentrations after clomiphene (mean difference: 11.56 nmol/L) and enclomiphene (mean difference: 7.50 nmol/L) was observed. The authors concluded that treatment with SERMs may be an effective alternative to testosterone replacement therapy in men with obesity-related FH [63].

It should be strongly emphasized that currently SERMs and AI are not recommended for the treatment of hypogonadism [53, 64]. We currently have few placebo-controlled clinical trials with AIs, and there are legitimate concerns about the lack of beneficial effects on body composition [65] and adverse effects on bone mineral density [66]. There are also no large studies with SERMs, and despite showing a beneficial effect on T concentrations and lean body mass, unfortunately, SERMs can reduce the secretion of insulin-like growth factor-1 (IGF-1) and thus inhibit anabolism, increase SHBG levels, and finally reduce T bioavailability [67].

#### ***Testosterone replacement therapy (TRT)***

A lot of clinical trials have been conducted evaluating the effect of TRT in obese men. The results of these studies are often conflicting because the study groups were not homogeneous, different definitions of hypogonadism were used, and different T formulations and doses were applied. Also, the participant recruitment strategies and limited statistical power of most of these studies make their interpretation difficult. Some of these studies reported beneficial effects of T administration, but most were performed in men with diabetes or metabolic syndrome, and the main endpoints were metabolic control of diabetes, fasting glucose, lipids, HbA<sub>1c</sub> levels, and cardiovascular risk of TRT. Meta-analyses of these studies suggested significant but small beneficial effects on glucose metabolism, but BMI

was not an inclusion criterion or major endpoint [68]. Many studies have shown the beneficial effects TRT on body composition and insulin sensitivity in men with low T and an unfavourable metabolic profile; however, the most common changes are reduction in fat mass (but more in subcutaneous than visceral depots), an increase in lean mass, and improved insulin sensitivity.

The latest systematic review published in 2021, based on 16 studies, assessed the impact of TRT in obese men having low T levels, revealed that TRT led to a 2-kg lean body mass gain and slightly improved low-density lipoprotein (LDL). TRT was also effective for waist circumference and BMI reduction; however, large between-study heterogeneity was found, with 95% prediction intervals crossing the null effect line. The mean age of participants significantly modified the effect of TRT on weight loss [69].

FH should be diagnosed only after exclusion of organic causes of hypogonadism and based on the presence of clinical symptoms or signs of T deficiency in combination with consistently low morning serum T concentrations. In addition to morning total T, LH should also be measured in all patients with suspected FH to differentiate between the primary and secondary causes. The latest recommendations published by the European Academy of Andrology (EAA) recommend against TRT as a treatment for weight reduction in obese men [53]. The authors note that currently randomized clinical trials specifically designed to study the effects of TRT on weight reduction in obese men are not available, and TRT improves body composition without any change in total bodyweight or BMI. EAA also recommend against TRT in men with FH who desire fertility, because TRT suppresses gonadotrophins and endogenous T secretion as well as spermatogenesis. The EAA recommends lifestyle changes, including physical exercise and weight reduction, in overweight and obese men with FH because weight loss may increase T concentrations [53].

### GLP-1 analogue treatment

GLP1 receptor agonists are linked to progressive and sustained weight loss in subjects with obesity. Animal models have demonstrated that GLP1 might even have a direct impact on the HPT axis; however, these observations have not yet been confirmed in men [71]. Nevertheless, studies have been conducted to evaluate the effects of liraglutide in obese men with FH and poor response to lifestyle changes. In the first preliminary study the effects of liraglutide (3 mg/daily) on T levels were compared to those of TRT (1% T gel) in a 16-week study with 15 obese men (aged  $46.5 \pm 10.9$  years, BMI  $41.2 \pm 8.4$  kg/m<sup>2</sup>). Liraglutide, but not TRT, induced a 6% reduction in weight, and both treatments

improved sexual symptoms and significantly increased T concentrations, although the increase was more evident with T gel (5.9 vs. 2.6 nmol/L with liraglutide). Liraglutide treatment resulted in a significant increase in LH and FSH levels [11].

Because TRT is contraindicated in men with FH who desire fertility, the effects of 4-month treatment with liraglutide on reproductive and sexual function in obese men with FH, who are of childbearing age, was investigated in 110 men (age 18–35 years) [72]. Results of liraglutide treatment (3 mg daily) were compared to gonadotropin treatment and TRT. Patients treated with liraglutide showed significant improvement in conventional sperm parameters and erectile function compared to baseline and men treated with gonadotropins, as well as had higher levels of T, LH, FSH, and SHBG levels. TRT effectively improved erections but significantly inhibited the release of LH and FSH. This study showed the efficacy of a GLP1 analogue for the treatment of male patients with FH who desire fertility. These results were confirmed in a recent randomized controlled trial, which evaluated the influence of GLP-1 analogue and exercise on semen parameters, which were previously increased by diet-induced weight loss. A total of 56 men (18 to 65 years of age, and BMI between 32 and 43 kg/m<sup>2</sup>) were included in the study and assigned to an initial 8-week low-calorie diet (800 kcal/day) followed by 52 weeks of GLP-1 analogue treatment. The men lost on average 16.5 kg body weight during the low-calorie diet, which increased the sperm concentration 1.49-fold and sperm count 1.41-fold. These improvements were maintained for 52 weeks in men who maintained the weight loss, and the effectiveness of GLP-1 analogues was similar to that of exercising. The semen volume, sperm motility, and motile sperm count did not change [73].

## Conclusions

1. FH and fertility disorders are common consequences of obesity in men.
2. ED is a common symptom in obese and especially hypogonadal men.
3. FH should be diagnosed only after exclusion of organic causes of hypogonadism and based on the presence of clinical symptoms or signs of T deficiency in combination with consistently low morning serum T concentrations. In addition to morning total T, LH should also be measured in all patients with suspected FH, to differentiate between the primary and secondary causes.
4. Lifestyle changes, including physical exercise and weight reduction, in obese men with FH are recommended.



5. TRT is contraindicated in obese men with FH, especially in those who desire fertility.
6. SERMs and AI are effective in improving sperm quality, but their usefulness in the treatment of FH is controversial and not supported by randomized trials.
7. GLP-1 analogues appear to be effective and safe in the treatment of FH and infertility in obese men, but more randomized trials are needed.

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### Conflict of interest

None declared.

## References

8. World Health Organization. Obesity and overweight, 2018. [www.who.int/news-room/fact-sheets/detail/obesity-and-overweight](http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight).
9. Wojtyński B, Goryński P. Sytuacja zdrowotna ludności Polski i jej uwarunkowania. Narodowy Instytut Zdrowia Publicznego — Państwowy Zakład Higieny, Warszawa 2020.
10. Grossmann M, Matsumoto AM. A Perspective on Middle-Aged and Older Men With Functional Hypogonadism: Focus on Holistic Management. *J Clin Endocrinol Metab.* 2017; 102(3): 1067–1075, doi: [10.1210/jc.2016-3580](https://doi.org/10.1210/jc.2016-3580), indexed in Pubmed: [28359097](https://pubmed.ncbi.nlm.nih.gov/28359097/).
11. Tajar A, Forti G, O'Neill TW, et al. EMAS Group. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol Metab.* 2010; 95(4): 1810–1818, doi: [10.1210/jc.2009-1796](https://doi.org/10.1210/jc.2009-1796), indexed in Pubmed: [20173018](https://pubmed.ncbi.nlm.nih.gov/20173018/).
12. De Lorenzo A, Noce A, Moriconi E, et al. MOSH Syndrome (Male Obesity Secondary Hypogonadism): Clinical Assessment and Possible Therapeutic Approaches. *Nutrients.* 2018; 10(4), doi: [10.3390/nu10040474](https://doi.org/10.3390/nu10040474), indexed in Pubmed: [29649106](https://pubmed.ncbi.nlm.nih.gov/29649106/).
13. Fui MN, Dupuis P, Grossmann M. Lowered testosterone in male obesity: mechanisms, morbidity and management. *Asian J Androl.* 2014; 16(2): 223–231, doi: [10.4103/1008-682X.122365](https://doi.org/10.4103/1008-682X.122365), indexed in Pubmed: [24407187](https://pubmed.ncbi.nlm.nih.gov/24407187/).
14. Cohen PG. The hypogonadal-obesity cycle: role of aromatase in modulating the testosterone-estradiol shunt—a major factor in the genesis of morbid obesity. *Med Hypotheses.* 1999; 52(1): 49–51, doi: [10.1054/mehy.1997.0624](https://doi.org/10.1054/mehy.1997.0624), indexed in Pubmed: [10342671](https://pubmed.ncbi.nlm.nih.gov/10342671/).
15. Saylor PJ, Smith MR, Saylor PJ, et al. Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol.* 2009; 181(5): 1998–2006; discussion 2007, doi: [10.1016/j.juro.2009.01.047](https://doi.org/10.1016/j.juro.2009.01.047), indexed in Pubmed: [19286225](https://pubmed.ncbi.nlm.nih.gov/19286225/).
16. Escobar-Morreale HF, Santacruz E, Luque-Ramírez M, et al. Prevalence of 'obesity-associated gonadal dysfunction' in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis. *Hum Reprod Update.* 2017; 23(4): 390–408, doi: [10.1093/humupd/dmx012](https://doi.org/10.1093/humupd/dmx012), indexed in Pubmed: [28486593](https://pubmed.ncbi.nlm.nih.gov/28486593/).
17. Sultan S, Patel AG, El-Hassani S, et al. Male Obesity Associated Gonadal Dysfunction and the Role of Bariatric Surgery. *Front Endocrinol (Lausanne).* 2020; 11: 408, doi: [10.3389/fendo.2020.00408](https://doi.org/10.3389/fendo.2020.00408), indexed in Pubmed: [32636807](https://pubmed.ncbi.nlm.nih.gov/32636807/).
18. Jensterle M, Podbregar A, Gorcar K, et al. Effects of liraglutide on obesity-associated functional hypogonadism in men. *Endocr Connect.* 2019; 8(3): 195–202, doi: [10.1530/EC-18-0514](https://doi.org/10.1530/EC-18-0514), indexed in Pubmed: [30707677](https://pubmed.ncbi.nlm.nih.gov/30707677/).
19. Narinx N, David K, Walravens J, et al. Role of sex hormone-binding globulin in the free hormone hypothesis and the relevance of free testosterone in androgen physiology. *Cell Mol Life Sci.* 2022; 79(11): 543, doi: [10.1007/s00018-022-04562-1](https://doi.org/10.1007/s00018-022-04562-1), indexed in Pubmed: [36205798](https://pubmed.ncbi.nlm.nih.gov/36205798/).
20. Goldman AL, Bhasin S, Wu FCW, et al. A Reappraisal of Testosterone's Binding in Circulation: Physiological and Clinical Implications. *Endocr Rev.* 2017; 38(4): 302–324, doi: [10.1210/er.2017-00025](https://doi.org/10.1210/er.2017-00025), indexed in Pubmed: [28673039](https://pubmed.ncbi.nlm.nih.gov/28673039/).
21. Grossmann M. Hypogonadism and male obesity: Focus on unresolved questions. *Clin Endocrinol (Oxf).* 2018; 89(1): 11–21, doi: [10.1111/cen.13723](https://doi.org/10.1111/cen.13723), indexed in Pubmed: [29683196](https://pubmed.ncbi.nlm.nih.gov/29683196/).
22. Grossmann M. Testosterone and glucose metabolism in men: current concepts and controversies. *J Endocrinol.* 2014; 220(3): R37–R55, doi: [10.1530/JOE-13-0393](https://doi.org/10.1530/JOE-13-0393), indexed in Pubmed: [24353306](https://pubmed.ncbi.nlm.nih.gov/24353306/).
23. Clarke H, Dhillo WS, Jayasena CN. Comprehensive Review on Kisspeptin and Its Role in Reproductive Disorders. *Endocrinol Metab (Seoul).* 2015; 30(2): 124–141, doi: [10.3803/EnM.2015.30.2.124](https://doi.org/10.3803/EnM.2015.30.2.124), indexed in Pubmed: [26194072](https://pubmed.ncbi.nlm.nih.gov/26194072/).
24. Souto P, Belo S, Oliveira SC, et al. AMTCO Group. Insulin resistance and sex hormone-binding globulin are independently correlated with low free testosterone levels in obese males. *Andrologia.* 2018; 50(7): e13035, doi: [10.1111/and.13035](https://doi.org/10.1111/and.13035), indexed in Pubmed: [29744905](https://pubmed.ncbi.nlm.nih.gov/29744905/).
25. Haffner SM, Shaten J, Stern MP, et al. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. *Am J Epidemiol.* 1996; 143(9): 889–897, doi: [10.1093/oxfordjournals.aje.a008832](https://doi.org/10.1093/oxfordjournals.aje.a008832), indexed in Pubmed: [8610702](https://pubmed.ncbi.nlm.nih.gov/8610702/).
26. Rąbiejewski M, Papierska L, Zgliczyński W, et al. The incidence of hypogonadotropic hypogonadism in type 2 diabetic men in Polish population. *Biomed Res Int.* 2013; 2013: 767496, doi: [10.1155/2013/767496](https://doi.org/10.1155/2013/767496), indexed in Pubmed: [24222915](https://pubmed.ncbi.nlm.nih.gov/24222915/).
27. Ghaderpour S, Ghiasi R, Heydari H, et al. The relation between obesity, kisspeptin, leptin, and male fertility. *Horm Mol Biol Clin Invest.* 2021; 43(2): 235–247, doi: [10.1515/hmbci-2021-0058](https://doi.org/10.1515/hmbci-2021-0058), indexed in Pubmed: [34931507](https://pubmed.ncbi.nlm.nih.gov/34931507/).
28. Harter CJL, Kavanagh GS, Smith JT. The role of kisspeptin neurons in reproduction and metabolism. *J Endocrinol.* 2018; 238(3): R173–R183, doi: [10.1530/JOE-18-0108](https://doi.org/10.1530/JOE-18-0108), indexed in Pubmed: [30042117](https://pubmed.ncbi.nlm.nih.gov/30042117/).
29. Bianchi VE. The Anti-Inflammatory Effects of Testosterone. *J Endocr Soc.* 2019; 3(1): 91–107, doi: [10.1210/je.2018-00186](https://doi.org/10.1210/je.2018-00186), indexed in Pubmed: [30582096](https://pubmed.ncbi.nlm.nih.gov/30582096/).
30. Sarchielli E, Comeglio P, Squacco R, et al. Tumor Necrosis Factor- $\alpha$  Impairs Kisspeptin Signaling in Human Gonadotropin-Releasing Hormone Primary Neurons. *J Clin Endocrinol Metab.* 2017; 102(1): 46–56, doi: [10.1210/jc.2016-2115](https://doi.org/10.1210/jc.2016-2115), indexed in Pubmed: [27736314](https://pubmed.ncbi.nlm.nih.gov/27736314/).
31. Fernandez CJ, Chacko EC, Pappachan JM. Male Obesity-related Secondary Hypogonadism - Pathophysiology, Clinical Implications and Management. *Eur Endocrinol.* 2019; 15(2): 83–90, doi: [10.17925/EE.2019.15.2.83](https://doi.org/10.17925/EE.2019.15.2.83), indexed in Pubmed: [31616498](https://pubmed.ncbi.nlm.nih.gov/31616498/).
32. Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care.* 2007; 30(2): 234–238, doi: [10.2337/dc06-1579](https://doi.org/10.2337/dc06-1579), indexed in Pubmed: [17259487](https://pubmed.ncbi.nlm.nih.gov/17259487/).
33. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care.* 2010; 33(6): 1186–1192, doi: [10.2337/dc09-1649](https://doi.org/10.2337/dc09-1649), indexed in Pubmed: [20200299](https://pubmed.ncbi.nlm.nih.gov/20200299/).
34. Mohr BA, Bhasin S, Link CL, et al. The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. *Eur J Endocrinol.* 2006; 155(3): 443–452, doi: [10.1530/eje.1.02241](https://doi.org/10.1530/eje.1.02241), indexed in Pubmed: [16914599](https://pubmed.ncbi.nlm.nih.gov/16914599/).
35. Brand JS, Rovers MM, Yeap BuB, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. *PLoS One.* 2014; 9(7): e100409, doi: [10.1371/journal.pone.0100409](https://doi.org/10.1371/journal.pone.0100409), indexed in Pubmed: [25019163](https://pubmed.ncbi.nlm.nih.gov/25019163/).
36. Antonio L, Wu FCW, O'Neill TW, et al. European Male Ageing Study Group. Low Free Testosterone Is Associated with Hypogonadal Signs and Symptoms in Men with Normal Total Testosterone. *J Clin Endocrinol Metab.* 2016; 101(7): 2647–2657, doi: [10.1210/jc.2015-4106](https://doi.org/10.1210/jc.2015-4106), indexed in Pubmed: [26909800](https://pubmed.ncbi.nlm.nih.gov/26909800/).
37. Nielsen TL, Hagen C, Wraae K, et al. Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. *J Clin Endocrinol Metab.* 2007; 92(7): 2696–2705, doi: [10.1210/jc.2006-1847](https://doi.org/10.1210/jc.2006-1847), indexed in Pubmed: [17426100](https://pubmed.ncbi.nlm.nih.gov/17426100/).
38. Di Vincenzo A, Busetto L, Vettor R, et al. Obesity, Male Reproductive Function and Bariatric Surgery. *Front Endocrinol (Lausanne).* 2018; 9: 769, doi: [10.3389/fendo.2018.00769](https://doi.org/10.3389/fendo.2018.00769), indexed in Pubmed: [30619096](https://pubmed.ncbi.nlm.nih.gov/30619096/).
39. Wu FCW, Tajar A, Beynon JM, et al. EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med.* 2010; 363(2): 123–135, doi: [10.1056/NEJMoa0911101](https://doi.org/10.1056/NEJMoa0911101), indexed in Pubmed: [20554979](https://pubmed.ncbi.nlm.nih.gov/20554979/).
40. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med.* 2003; 139(3): 161–168, doi: [10.7326/0003-4819-139-3-200308050-00005](https://doi.org/10.7326/0003-4819-139-3-200308050-00005), indexed in Pubmed: [12899583](https://pubmed.ncbi.nlm.nih.gov/12899583/).
41. Araujo AB, Johannes CB, Feldman HA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med.* 2000; 30(4): 328–338, doi: [10.1006/pmed.2000.0643](https://doi.org/10.1006/pmed.2000.0643), indexed in Pubmed: [10731462](https://pubmed.ncbi.nlm.nih.gov/10731462/).
42. Rąbiejewski M, Papierska L, Kozakowski J, et al. The high prevalence of testosterone deficiency in population of Polish men over 65 years with

- erectile dysfunctions. *Aging Male*. 2012; 15(4): 258–262, doi: [10.3109/13685538.2012.729233](#), indexed in Pubmed: [23094956](#).
43. Rabijewski M, Papierska L, Kuczerowski R, et al. Hormonal determinants of erectile dysfunction and lower urinary tract symptoms in middle-aged and elderly men with prediabetes. *Aging Male*. 2015; 18(4): 256–264, doi: [10.3109/13685538.2015.1083972](#), indexed in Pubmed: [26444448](#).
  44. Pizzol D, Smith L, Fontana L, et al. Associations between body mass index, waist circumference and erectile dysfunction: a systematic review and META-analysis. *Rev Endocr Metab Disord*. 2020; 21(4): 657–666, doi: [10.1007/s11154-020-09541-0](#), indexed in Pubmed: [32002782](#).
  45. Wang JM, Li ZF, Yang WX, et al. Follicle-stimulating hormone signaling in Sertoli cells: a licence to the early stages of spermatogenesis. *Reprod Biol Endocrinol*. 2022; 20(1): 97, doi: [10.1186/s12958-022-00971-w](#), indexed in Pubmed: [35780146](#).
  46. Li X, Li H, Jia L, et al. Oestrogen action and male fertility: experimental and clinical findings. *Cell Mol Life Sci*. 2015; 72(20): 3915–3930, doi: [10.1007/s00018-015-1981-4](#), indexed in Pubmed: [26160724](#).
  47. Carrageta DE, Oliveira PF, Alves MG, et al. Obesity and male hypogonadism: Tales of a vicious cycle. *Obes Rev*. 2019; 20(8): 1148–1158, doi: [10.1111/obr.12863](#), indexed in Pubmed: [31035310](#).
  48. Leisegang K, Sengupta P, Agarwal A, et al. Obesity and male infertility: Mechanisms and management. *Andrologia*. 2021; 53(1): e13617, doi: [10.1111/andr.13617](#), indexed in Pubmed: [32399992](#).
  49. LA Padula D, Zavaglia L, Hamad T, et al. Leptin effects: focusing on the relationship between obesity and male infertility. *Minerva Endocrinol (Torino)*. 2022 [Epub ahead of print], doi: [10.23736/S2724-6507.22.03901-X](#), indexed in Pubmed: [36251021](#).
  50. Paul C, Melton DW, Saunders PTK. Do heat stress and deficits in DNA repair pathways have a negative impact on male fertility? *Mol Hum Reprod*. 2008; 14(1): 1–8, doi: [10.1093/molehr/gam089](#), indexed in Pubmed: [18175790](#).
  51. Panner Selvam MK, Ambar RF, Agarwal A, et al. Etiologies of sperm DNA damage and its impact on male infertility. *Andrologia*. 2021; 53(1): e13706, doi: [10.1111/andr.13706](#), indexed in Pubmed: [32559347](#).
  52. Alahmar AT, Singh R, Palani A, et al. Coenzyme Q10, oxidative stress, and male infertility: A review. *Clin Exp Reprod Med*. 2021; 48(2): 97–104, doi: [10.5653/ceerm.2020.04175](#), indexed in Pubmed: [34078005](#).
  53. Sengupta P, Dutta S, Krajewska-Kulak E. The Disappearing Sperms: Analysis of Reports Published Between 1980 and 2015. *Am J Mens Health*. 2017; 11(4): 1279–1304, doi: [10.1177/1557988316643383](#), indexed in Pubmed: [27099345](#).
  54. Chavarro JE, Toth TL, Wright DL, et al. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril*. 2010; 93(7): 2222–2231, doi: [10.1016/j.fertnstert.2009.01.100](#), indexed in Pubmed: [19261274](#).
  55. Sermondade N, Faure C, Fezeu L, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update*. 2013; 19(3): 221–231, doi: [10.1093/humupd/dms050](#), indexed in Pubmed: [23242914](#).
  56. Salas-Huetos A, Maghsoumi-Norouzabad L, James ER, et al. Male adiposity, sperm parameters and reproductive hormones: An updated systematic review and collaborative meta-analysis. *Obes Rev*. 2021; 22(1): e13082, doi: [10.1111/obr.13082](#), indexed in Pubmed: [32705766](#).
  57. Wang S, Sun J, Wang J, et al. Does obesity based on body mass index affect semen quality?—A meta-analysis and systematic review from the general population rather than the infertile population. *Andrologia*. 2021; 53(7): e14099, doi: [10.1111/andr.14099](#), indexed in Pubmed: [34028074](#).
  58. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, et al. Subfecundity in overweight and obese couples. *Hum Reprod*. 2007; 22(6): 1634–1637, doi: [10.1093/humrep/dem035](#), indexed in Pubmed: [17344224](#).
  59. Bibi R, Jahan S, Afsar T, et al. The influence of paternal overweight on sperm chromatin integrity, fertilization rate and pregnancy outcome among males attending fertility clinic for IVF/ICSI treatment. *BMC Pregnancy Childbirth*. 2022; 22(1): 620, doi: [10.1186/s12884-022-04953-z](#), indexed in Pubmed: [35931982](#).
  60. Corona G, Goulis DG, Huhtaniemi I, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: Endorsing organization: European Society of Endocrinology. *Andrology*. 2020; 8(5): 970–987, doi: [10.1111/andr.12770](#), indexed in Pubmed: [32026626](#).
  61. Camacho EM, Huhtaniemi IT, O'Neill TW, et al. EMAS Group. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *Eur J Endocrinol*. 2013; 168(3): 445–455, doi: [10.1530/EJ-12-0890](#), indexed in Pubmed: [23425925](#).
  62. Corona G, Rastrelli G, Morelli A, et al. Treatment of Functional Hypogonadism Besides Pharmacological Substitution. *World J Mens Health*. 2020; 38(3): 256–270, doi: [10.5534/wjmh.190061](#), indexed in Pubmed: [31496147](#).
  63. Corona G, Rastrelli G, Monami M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *Eur J Endocrinol*. 2013; 168(6): 829–843, doi: [10.1530/EJE-12-0955](#), indexed in Pubmed: [23482592](#).
  64. Emami MR, Safabakhsh M, Khorshidi M, et al. Effect of bariatric surgery on endogenous sex hormones and sex hormone-binding globulin levels: a systematic review and meta-analysis. *Surg Obes Relat Dis*. 2021; 17(9): 1621–1636, doi: [10.1016/j.soard.2021.05.003](#), indexed in Pubmed: [34187743](#).
  65. Xu J, Wu Q, Zhang Y, et al. Effect of Bariatric Surgery on Male Sexual Function: A Meta-Analysis and Systematic Review. *Sex Med*. 2019; 7(3): 270–281, doi: [10.1016/j.esxm.2019.06.003](#), indexed in Pubmed: [31302076](#).
  66. Lee Y, Dang JT, Switzer N, et al. Impact of Bariatric Surgery on Male Sex Hormones and Sperm Quality: a Systematic Review and Meta-Analysis. *Obes Surg*. 2019; 29(1): 334–346, doi: [10.1007/s11695-018-3557-5](#), indexed in Pubmed: [30382463](#).
  67. Gao Z, Liang Y, Yang S, et al. Bariatric Surgery Does Not Improve Semen Quality: Evidence from a Meta-analysis. *Obes Surg*. 2022; 32(4): 1341–1350, doi: [10.1007/s11695-022-05901-8](#), indexed in Pubmed: [35143010](#).
  68. Guo B, Li JJ, Ma YL, et al. Efficacy and safety of letrozole or anastrozole in the treatment of male infertility with low testosterone-estradiol ratio: A meta-analysis and systematic review. *Andrology*. 2022; 10(5): 894–909, doi: [10.1111/andr.13185](#), indexed in Pubmed: [35438843](#).
  69. Cannarella R, Condorelli RA, Mongioi LM, et al. Effects of the selective estrogen receptor modulators for the treatment of male infertility: a systematic review and meta-analysis. *Expert Opin Pharmacother*. 2019; 20(12): 1517–1525, doi: [10.1080/14656566.2019.1615057](#), indexed in Pubmed: [31120775](#).
  70. Di Giulio F, Castellini C, Tienforti D, et al. Erectile dysfunction in hyperuricemia: A prevalence meta-analysis and meta-regression study. *Andrology*. 2022; 10(1): 72–81, doi: [10.1111/andr.13088](#), indexed in Pubmed: [34347943](#).
  71. Jayasena CN, Anderson RA, Llahana S, et al. Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism. *Clin Endocrinol (Oxf)*. 2022; 96(2): 200–219, doi: [10.1111/cen.14633](#), indexed in Pubmed: [34811785](#).
  72. Burnett-Bowie SAM, Roupenian KC, Dere ME, et al. Effects of aromatase inhibition in hypogonadal older men: a randomized, double-blind, placebo-controlled trial. *Clin Endocrinol (Oxf)*. 2009; 70(1): 116–123, doi: [10.1111/j.1365-2265.2008.03327.x](#), indexed in Pubmed: [18616708](#).
  73. Burnett-Bowie SAM, McKay EA, Lee H, et al. Effects of aromatase inhibition on bone mineral density and bone turnover in older men with low testosterone levels. *J Clin Endocrinol Metab*. 2009; 94(12): 4785–4792, doi: [10.1210/jc.2009-0739](#), indexed in Pubmed: [19820017](#).
  74. Birzniece V, Sata A, Sutanto S, et al. Neuroendocrine regulation of growth hormone and androgen axes by selective estrogen receptor modulators in healthy men. *J Clin Endocrinol Metab*. 2010; 95(12): 5443–5448, doi: [10.1210/jc.2010-1477](#), indexed in Pubmed: [20843951](#).
  75. Cai X, Tian Ye, Wu T, et al. Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Asian J Androl*. 2014; 16(1): 146–152, doi: [10.4103/1008-682X.122346](#), indexed in Pubmed: [24369149](#).
  76. Mangolim AS, Brito LD, Nunes-Nogueira VD. Effectiveness of testosterone replacement in men with obesity: a systematic review and meta-analysis. *Eur J Endocrinol*. 2021; 186(1): 123–135, doi: [10.1530/EJE-21-0473](#), indexed in Pubmed: [34738915](#).
  77. Jensterle M, Podbregar A, Gorican K, et al. Effects of liraglutide on obesity-associated functional hypogonadism in men. *Endocr Connect*. 2019; 8(3): 195–202, doi: [10.1530/EC-18-0514](#), indexed in Pubmed: [30707677](#).
  78. Izzi-Engbeaya C, Jones S, Crustna Y, et al. Effects of Glucagon-like Peptide-1 on the Reproductive Axis in Healthy Men. *J Clin Endocrinol Metab*. 2020; 105(4): 1119–1125, doi: [10.1210/clinem/dgaa072](#), indexed in Pubmed: [32052032](#).
  79. La Vignera S, Condorelli RA, Calogero AE, et al. Sexual and Reproductive Outcomes in Obese Fertile Men with Functional Hypogonadism after Treatment with Liraglutide: Preliminary Results. *J Clin Med*. 2023; 12(2), doi: [10.3390/jcm12020672](#), indexed in Pubmed: [36675601](#).
  80. Andersen E, Juhl CR, Kjeller ET, et al. Sperm count is increased by diet-induced weight loss and maintained by exercise or GLP-1 analogue treatment: a randomized controlled trial. *Hum Reprod*. 2022; 37(7): 1414–1422, doi: [10.1093/humrep/deac096](#), indexed in Pubmed: [35580859](#).