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REVIEW

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How much does obesity affect the male reproductive function?

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Abstract

Obesity is considered a worldwide epidemic disease. Many pathological conditions have been associated to obesity but the evidence relating to impaired fertility in males with obesity are contrasting. The aim of this review was to evaluate the interplay between obesity and male fertility, analyzing evidence from in vitro and in vivo studies to clinical trials. Obesity seems to be responsible of secondary hypogonadism. Here, we propose a new classification including central, peripheral and testicular factors that may affect the hypothalamic-pituitary-gonadal axis. Moreover, some studies demonstrated a direct action of obesity on sperm count and sperm characteristics, mediated by impaired Sertoli cells function, increased scrotal temperature, oxidative stress and accumulation of toxic substances and liposoluble endocrine disruptors in fat tissue. Recent studies have explored obesity-related epigenetic effects in sperm cells which may cause diseases in offspring. Moreover, not only in females but also males, obesity has been linked to reduced outcomes of in vitro fertilization, with a reduction of pregnancy rate and an increase of pregnancy loss. Finally, we reviewed the effects of weight modifications through diet or bariatric surgery on obesity-related reproductive dysfunction. In this regard, several studies have demonstrated that weight loss has been associated with a restoration of gonadal hormones levels.

Introduction

Obesity is a worldwide epidemic disease, affecting more than 650 million adults [1]. Overall, about 13% of the world adult population were classed as being obese in 2016 [1]. According to the World Health Organization, excessive weight and obesity are defined as abnormal accumulation of fat that represents a health risk [2]. Obesity has been reported to be associated with cardiovascular disease, sleep apnea, osteoarthritis and some types of cancer [3]. Further, erectile dysfunction, low testosterone concentrations and infertility can also be observed.

The association between obesity and male reproductive dysfunction is reported in epidemiological studies [4]. Azoospermia and oligospermia are more prevalent among males with obesity compared with those without obesity [5]. Some studies from northern Europe report an adjusted odds ratio for infertility at 12 months between 1.36 and 1.53 for males with obesity compared to those of normal weight [6]. Obesity is associated with an increased time to conception and reduced pregnancy rates [7]. This review explores the impact of obesity on male reproductive function providing an overview of the human studies and the potential treatment.

Obesity and hormonal disorders

The best known effect of obesity on male reproductive function is secondary hypogonadism [8]. This is characterized by low testosterone (<12.1 nmol/l) associated with signs and symptoms of hypogonadism, such as reduced sexual desire and activity, decreased spontaneous erections, loss of body (axillary and pubic) hair, reduced shaving, impaired spermatogenesis with reduced levels of inhibin B and low/normal FSH and LH concentration [9].

Here, we outline all the factors hypothesized to be responsible for secondary hypogonadism in males with

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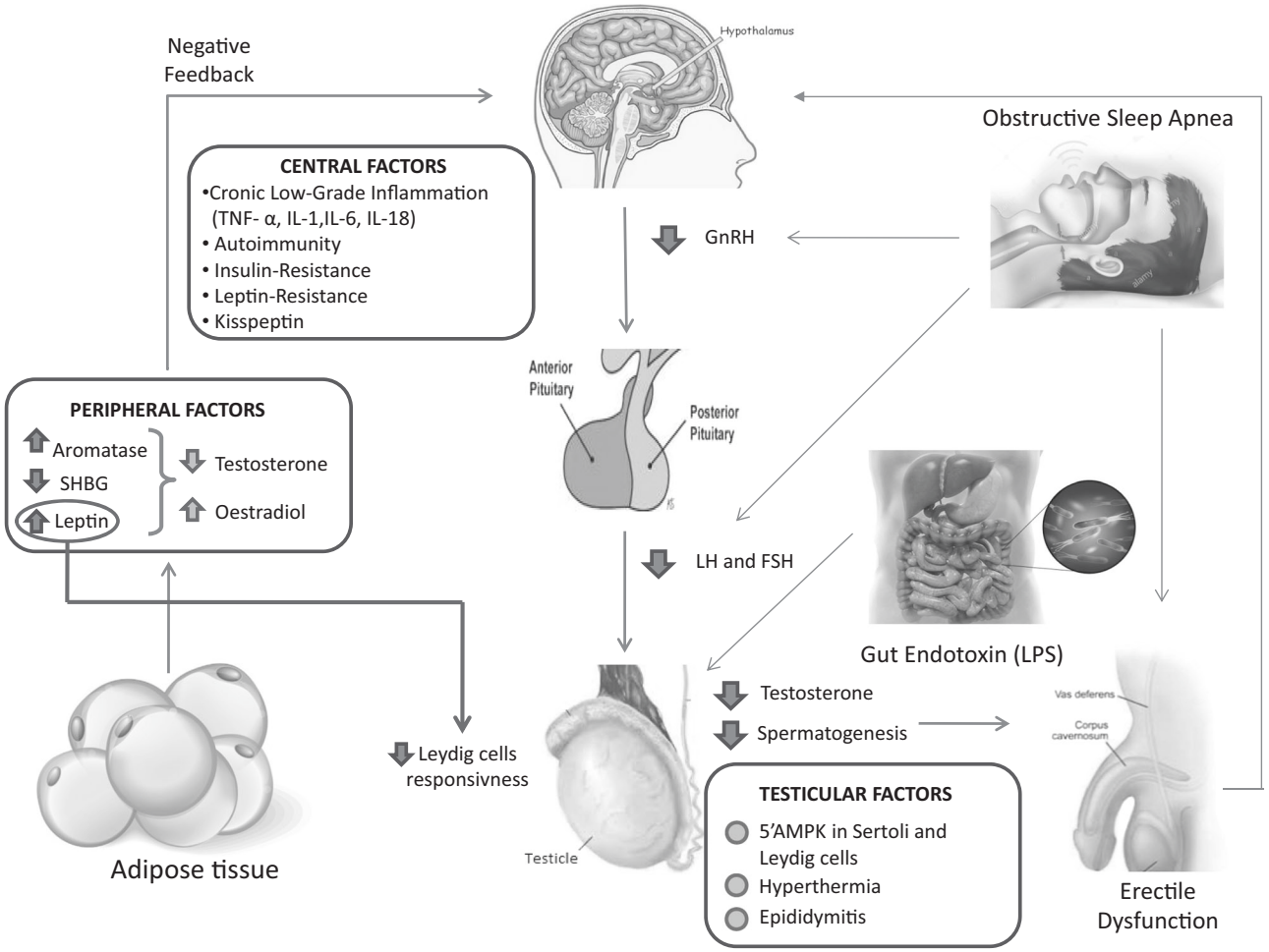

Fig. 1 Central, peripheral and testicular factors that contribute to impair the HPG axis function

obesity. In particular, we propose a new classification in which we identify some central, peripheral and testicular factors (Fig. 1).

Central factors

With the term 'central factors' we mean all the mechanisms and the disorders affecting the hypothalamic—pituitary axis activity. The main mediators originate from excess of adipose tissue, which induces a chronic inflammation state associated with an insulin and leptin resistance [10].

Inflammatory mediators

Tumour necrosis factor (TNF-α) and Interleukin-1B (IL-1B) are inflammatory mediators that contribute to low grade chronic inflammation and at the same time to suppress hypothalamic GnRH secretion and LH secretion in vitro [11]. IL-1 (especially IL-1β, more than IL1-α) potently suppresses LH release through blockade of GnRH secretion [12], by inhibiting the translational efficiency of the GnRH mRNA [13]. The prospective, randomized, placebo-controlled trial TestIL is currently ongoing to investigate the hypothesis that the blockade of IL-1 activity diminishes its inhibitory effect on the hypothalamic-hypophyseal-gonadal (HPG) axis and increases testosterone levels in men with metabolic syndrome (Clinical Trial.gov, NCT02672592). The role of IL-6 is still debated. Although an in vivo study reported an inhibitory effect of IL-6 on LH secretion [14], other reports did not confirm this effect [14]. However, in vitro studies demonstrated sex-related differences in the effects of IL-6 on pituitary LH release in rats [15]. Several in vivo studies demonstrated that TNF-α plays an inhibitory effect on the GnRH-LH system [13, 14]. Also C-reactive protein (CRP) may contribute to the suppression of the HPG axis and may also worsen insulin resistance interfering with insulin signal transduction [16].

Insulin resistance

Insulin resistance may be considered the second most relevant causative factor in obesity-induced hypogonadism.

It is known from cell culture studies that insulin stimulates the HPG axis activity at several levels, i.e., hypothalamic, pituitary and testicular levels [16]. Insulin resistance may also affect hypothalamic neurons and consequently the GnRH secretion [17]. This hypothesis is supported by some studies on animal models. In particular, the neuron-specific insulin receptor knock-out male mice show a 60–90% decrease in serum LH concentration [18]. Therefore, the maintenance of the functional integrity of the HPG axis needs a correct insulin metabolic pathway in the brain.

Leptin resistance

Leptin is a hormone secreted by adipocytes that not only stimulates the satiety center but also acts as a neuroendocrine hormone in regulating sexual maturation and reproduction [9]. Leptin may act as a central or peripheral factor (see below). The central role is due to the presence of leptin receptors on kiss1 neurons that are able to stimulate GnRH secretion. Leptin is also able to negatively control Neuropeptide Y(NPY) expression and then to prevent the NPY neurons from inhibiting GnRH release [19]. Some authors hypothesized that the leptin excess in obese males and in particular in those with impaired fertility drives the HPG axis to become leptin resistant [20]. This effect results in reduced GnRH, FSH and LH release and consequently impaired spermatogenesis.

Kisspeptin

Kisspeptin is a hypothalamic peptide encoded by the KiSS1 gene, a gene that was first described in 1996 as associated with human malignant melanoma [21]. Since its first description, kisspeptin was recognized as an important neuromodulator with a key role in the HPG axis and fertility control. In humans, most of the kisspeptin cells are localized at the hypothalamic level, especially in the infundibular nucleus and in the rostral preoptic area [22], even if kisspeptin traces have been identified also in peripheral tissues, as the testis, ovary, pancreas and small bowel. Through its G-protein coupled receptor KISS1R (also called GPR-54) kisspeptin increases delivery of GnRH into the portal circulation which enhances the secretion of LH and FSH from the anterior pituitary cells [23]. It has been shown that administration of exogenous intravenous kisspeptin-54 infusion in healthy men stimulated a significant increase of serum LH, FSH and testosterone concentrations compared with saline infusion [24]. In hypogonadal men with type 2 diabetes kisspeptin-10 infusion increased LH frequency and amplitude, with an associated increase in serum testosterone [25]. A decreased endogenous kisspeptin secretion plays a central role in mediating obesity-related hypogonadotropic hypogonadism (HH). Experimental studies have shown that a high fat diet (HFD) and central leptin resistance determine a marked decrease in kisspeptin expression both in the rostral periventricular region of the third ventricle and the arcuate nucleus in mice models [26]. Another experimental study showed that mice with diabetes type 1 had alteration in kiss1 and/or GPR-54 mRNA expression in both kisspeptin neurons and peripheral tissues (fat, pancreas and liver) [27]. This is an important issue for potential future pharmacological therapies based on kisspeptin analogue to treat HH.

Autoimmunity

It has been reported that there is an increased risk of some autoimmune diseases in people with obesity [28]. A possible role of pituitary autoimmunity as a pathophysiological mechanism for HH in obese males has so far not been investigated, but it may not be excluded, even because HH has been frequently observed in patients with autoimmune hypophysitis, positive for antipituitary antibodies targeting gonadotropin-secreting cells [29]. Moreover, pituitary antibodies to pituitary gonadotropin-secreting cells have been demonstrated in patients with type 2 diabetes mellitus (T2DM) [29]. Obese patients, on one hand, are prone to inflammatory processes due to increased levels of inflammatory mediators which can favour also pituitary autoimmunity [30], on the other hand they are prone to develop T2DM. On these bases, cross-sectional and longitudinal studies investigating the occurrence of pituitary autoimmunity in obese patients is advisable.

Peripheral factors

We mean with this term all the factors and conditions determining a peripheral change in sexual hormones concentrations and consequently affecting central and testicular function.

Leptin

Leptin is higher in obese than in non-obese males. The peripheral effects include a direct possible inhibitory effect on Leydig cells and then on testosterone production [19]. Moreover, leptin may reduce the Leydig cell responsiveness to LH stimulation mediated by the expression of its receptor in testicular tissue and in seminal fluid. Increase of leptin levels might directly affect spermatogenesis and seems to favor germ cell apoptosis in testes [31]. In human males, leptin is negatively correlated with total and free testosterone levels resulting a good predictor of impaired androgen secretion in people with obesity [31].

Sex hormone-binding globulin (SHBG)

SHBG, released by the liver, binds testosterone with high affinity and its concentrations are inversely correlated with body mass index (BMI) [32]. Obese males who develop insulin resistance and consequently hyperinsulinemia are at higher risk of low SHBG concentrations [33], because hyperinsulinemia suppresses hepatic production of SHBG [17]. The reduction of SHBG levels causes also a decrease in testosterone concentrations affecting its half-life [34], and an increased availability of free testosterone levels, a good substrate for aromatase to be converted to oestradiol. Indeed, aromatase activity is abundant in adipose tissue with consequent higher conversion of testosterone into oestradiol (testosterone-oestradiol shunt) [35]. The reduction of SHBG and the increase of aromatase activity determine a rise in oestradiol concentrations that have an inhibiting effect on central function (hypothalamic-pituitary function) [18].

Erectile dysfunction

Erectile dysfunction (ED) is a frequent complication [33] in men with obesity. Some studies show that obesity and, in particular, central obesity is associated with atherogenic ED [33]. Waist circumference has been shown to be a better predictor of ED than BMI [36]. We decided to include ED in the list of peripheral factors involved in hormonal dysfunction because of its role on coital frequency and consequently on testosterone levels and fertility [4]. In this regard, we support the hypothesis that sexual behaviour can exert a feedback action to hormone levels [37]: orgasmic frequency in males, whether through masturbation or coitus, is positively correlated with free and total testosterone [37].

Obstructive sleep apnea (OSA)

OSA is a condition characterized by frequent proximal airway obstruction resulting in apnea, hypopnea, oxygen desaturation [38]. OSA and the consequent sleep fragmentation produces a reversible dysfunction of the HPG axis [39]. Patients with OSA show lower free and total testosterone [40] with suppression of their nocturnal testosterone rise [41]. Moreover, it has to be considered a possible desynchronization of circadian rhythmicity with reduction of nocturnal increase of LH pulsatility and consequently reduction of testosterone secretion [42]. Obese patients usually have disorders in eating habits. This can induce further alterations of the internal clock [42] with consequent further impairment of HPG secretions. Finally, it may not be ignored that there is a possible desynchronization of the circannual testosterone rhythm in obese males, as occurring in other forms of hypogonadism [43].

Gut endotoxin

Obesity and high fat and high energy diets cause a breakdown in normal intestinal mucosal barrier function that then facilitates the passage of gut bacteria from the bowel lumen into the systemic circulation [44, 45]. This causes a chronic state of low grade inflammation that impairs testicular function and reproductive performance [45].

Testicular factors

In the previous sections, we described central and peripheral factors that may potentially affect testicular function. In this section we report obesity-related conditions developing into the scrotum that may locally affect testicular function.

The abdominal, suprapubic and medial thigh fat, wrapping the scrotum, leads to an increase in intrascrotal temperature determining an increased DNA fragmentation and an increased oxidative stress [9, 40, 46]. This negatively impacts on the sperm quality; the elevation in scrotal skin temperature has been associated with reduced sperm motility and concentration [46].

The hyperthermia may also affect other intrascrotal structures such as the epididymis that may be affected by inflammation [47]. The inflammation of the epididymis may impair epididymal function by altering sperm maturation and fertilization ability. The epididymal structure may be altered by inflammation (on one or both side) until cyst formation, ducts obstruction, scarring and fibrosis [46].The testes have a specific sensor of energy reserves, the 5′AMP-activated protein kinase (AMPK) sensitive to energy abundance as seen in obesity or energy restriction. It is present in Sertoli, Leydig and germinal cells. The sensor plays a crucial role in the regulation of gonadal steroidogenesis, in the proliferation and survival of somatic gonadal cells, as well as in the maturation of spermatozoa [47].

Obesity and spermatogenesis

In vitro and animal studies

Several lines of evidence from animal models have demonstrated a deleterious effect of obesity on sperm number and quality. In a study on an animal model of obesity, neonatal male rats were treated with monosodium glutamate, which is able to induce obesity causing alterations in the hypothalamic arcuate nucleus and impairing leptin and insulin signalling in this region. When compared to non-treated animals, obesity led to a significant decrease in the numbers of testicular spermatids and spermatozoa and a significant decrease in daily sperm production. Moreover, the acceleration of sperm transit time can affect spermatozoa maturation reducing

sperm quality of these rats [48]. Also sperm mobility in rats seems to be correlated to a decreased percent of sperm with progressive motility [49].

One possible mechanism by which obesity can affect sperm quality may be elevated oxidative stress in spermatozoa, causing elevated levels of sperm DNA damage and loss of function. In animal studies, the percentage of motile spermatozoa and intracellular reactive oxygen species (ROS) was decreased in the HFD group when compared with controls. Moreover, sperm DNA damage was also increased in the HFD group compared with the control group, and this parameter has been linked to poor reproductive outcome. The number of sperm bound to each oocyte was significantly reduced in the HFD group compared with controls and it resulted in significantly lower fertilization rates [50]. An interesting study has evaluated sperm quality in 4 groups of mice: control group, HFD group, restricted high fat diet group (RHFD) and restricted high fat diet group with antioxidants consumption (RHFDA) (astaxanthin, vitamins E and C group) [51]. Sperm number, viability, motility and normal morphology of the sperms in the HFD, RHFD, and RHFDA groups were significantly lower than the control group. Interestingly, sperm motility of the RHFDA group was decreased significantly compared to the control group but was significantly higher than HFD and RHFD groups, confirming that ROS may play a role in sperm alteration due to obesity [51].The detrimental effect of ROS on spermatogenesis has been demonstrated also in human spermatozoa, which are known to be susceptible to lipid peroxidation because of their high contents of unsaturated fatty acids [52].

Animal models have also been used to demonstrate the effects of obesity on sperm chromatin integrity [53]. In diet-induced obesity and leptin deficient obesity there was an increased sperm DNA fragmentation compared to lean mice [53]. The examination of the transcriptional response of a selection of marker genes in the testis by quantitative real-time PCR, showed moderate, but significant, up-regulation of the Cyp2e1, Cyp19a1, TNF and PPARγ genes in obese mice compared to lean mice, suggesting a local response in testicular cells to the HFD regimen with a potential impact on and spermatogenesis [53]. Obesity is also able to alter seminal vesicle fluid composition in a mouse model [54], increasing levels of insulin, leptin and reducing levels of oestradiol in seminal vesicle fluid.

Obesity reduced the quality of sperm also by changing inflammatory profile. Obese mice fed with HFD showed an increased mRNA expression levels of TNF-α, MCP-1, and F4/80 in testis while exenatide administration has shown to improve the quality of sperm through a reduction in the expression of pro-inflammatory cytokines [55]. Moreover, in vitro studies have demonstrated how inflammatory cytokines, as TNFα, IL-1, IL-6 produced by the white adipocytes, may affect directly spermatogenesis by various mechanisms: alteration in blood-testis barrier by impairing gap junctional communication in Sertoli cells [56], reduction in spermatogonia cellular differentiation, inhibition of meiotic DNA synthesis and reduction in sperm motility [57].

Human studies

Obesity and sperm concentration and quality

Several studies have investigated the impact of male obesity on the normal sperm physiological parameters, reporting controversial results. A reduction in sperm count have been demonstrated in obese subjects [58]. In a study on 225 male partners of pregnant women (16–32 weeks) who conceived naturally, obesity (BMI > 30 kg/m^2) was significantly related to total sperm count. Compared with those with BMI < 30 (n = 188), people with obesity (n = 35) had significantly lower total sperm count [59]. A study on 7630 male subjects in Taiwan (of which 31.4% were overweight or obese), investigating the correlation between BMI and other anthropometric indexes and semen quality [60], showed a significantly negative linear association between sperm concentration and BMI. In the same study, visceral adiposity, estimated by waist circumference, seemed to affect sperm concentration, sperm morphology but not sperm motility.

Coherently, another study on 2035 patients (18 underweight (1%), 839 (41%) normal weight, 909 (45%) overweight and 269 (13%) obese men), normal sperm morphology was significantly higher in normal-weight and underweight groups compared with overweight and obese groups, after correction for age, abstinence period and social deprivation [61]. Progressive motility was not associated with BMI [61].

In another study on 1248 subjects enrolled in a clinic for reproductive treatment or specialized in medical preconception care, overweight and obesity seemed to affect also sperm motility [62]. Overweight was negatively associated with the percentage of progressive motility type A and positively associated with the percentage of immotility type C. Obesity was negatively associated with sperm concentration and total motile sperm count after adjustment for age, ethnicity, active and passive smoking, alcohol, medication use and folate status [62]. Waist circumference ≥ 102 cm, a measure for central adiposity, was inversely associated with sperm concentration and total motile sperm count [62]. The negative impact of obesity on sperm quality is still poorly understood at the molecular level. An interesting study has recently analysed differences between the proteomes of spermatozoa obtained from obesity-associated asthenozoospermic and normozoospermic individuals using label-free quantitative LC-MS/MS proteomic analysis [63]. The study demonstrated declines in

ERp57 and ACTRT2 expression in obesity-associated asthenozoospermia; in fact these two protein may play critical roles in reducing sperm motility [63]. Obesity causes also a reduction in sperm volume compared with normal weight men [62].

On the contrary, other studies showed no effect of obesity on sperm parameters. For example, in a study on 2110 men attending infertility work-up sperm motility, morphology and concentration were not significantly different in groups with different BMI levels [3]. Similarly, in the LIFE study, BMI and waist circumference showed no correlation with semen concentration, motility, vitality, morphology or DNA fragmentation index. Only ejaculate volume and, consequently, total sperm count showed a linear decline with increasing BMI and waist circumference [64].

Three meta-analysis were performed to investigate the role of overweight and obesity on sperm parameters. The first one, published in 2010 by McDonald et al., analysed data on a total of 6793 men, failing to demonstrate a statistically significant relationship between BMI category and mean and median sperm concentration, mean and median total sperm count, mean semen volume or average sperm motility [65].

The meta-analysis published in 2013 by Sermondade et al., analysing data on 13,077 men, showed a J-shaped association between BMI and abnormal sperm count: underweight was associated with an increased but non-significant risk of abnormal sperm count, whereas overweight and obese men had a significantly elevated risk of abnormal sperm count compared with normal weight men [66].

The contrast between these two meta-analyses can be explained by the higher number of studies included in the second meta-analysis and the choice of dichotomizing sperm concentration (oligozoospermia or azoospermia) instead of trying to correlate BMI and sperm count. In 2017, another meta-analysis was performed [67], demonstrating a decreased total sperm count and semen volume in overweight patients and a decrease of total sperm count, sperm concentration and semen volume in obese patients, while no variation in sperm motility was demonstrated.

One mechanism proposed to explain why overweight and obesity may affect sperm quality is a direct action of obesity on Sertoli cell function, as indicated by reduced levels of inhibin-B in obese patients [68]. The effect of obesity on inhibin-B is established during puberty, because values of inhibin-B are normal in obese prepubertal boys. Considering that Sertoli cell is thought to support a finite number of germ cells, fewer Sertoli cells in obesity may predispose to a lower sperm count in adulthood [68].

The increase of testicular temperature caused by hip and abdominal fat tissue accumulation, but also by high fat content in scrotum area, has been hypothesized as cause of spermatogenesis disorders [69]. Obesity causes a reduction in the levels of some fatty acids in spermatozoa (docosahexaenoic acid, palmitic acid) associated with an increase in DNA fragmentation index and a reduction in total sperm count, sperm vitality and sperm motility [70]. Another potential underlying pathological mechanism of diminished reproductive performance in obese men could be sperm oxidative stress, which is increased in obese patients [71].

Finally, preferential accumulation of toxic substances and liposoluble endocrine disruptors in fat tissue could amplify the detrimental effects of these exogenous substances, as suggested by the direct correlation between serum organochlorine levels and BMI [72] (Fig. 2).

Obesity and other sperm parameters

Several studies have demonstrated a higher frequency of sperm DNA damage, in obese patients subjected to semen analysis at fertility clinics [73].

In a study on 330 male partners of subfertile couples presenting for semen analysis, DNA fragmentation rate, after adjustment for age and tobacco use, was significantly higher in obese men than in lean ones. No increase in DNA fragmentation was found in overweight men. Dividing fragmentation rate in 4 categories, OR for moving from one DNA fragmentation category to the next was 1.3 (0.8–2.1) for overweight and 2.4 (1.2–4.7) for obese men [74]. Another study by Fariello et al., showed that obese men had a higher percentage of sperm with high DNA fragmentation, evaluating visually DNA damage, as assessed by comet tail and nuclear intensity [75]. Another study on 520 healthy men (mean age 34.6 years) presenting for routine semen analysis demonstrated a significant and positive relation between BMI and DNA fragmentation index [76].

However, the current evidence is controversial. Rybar et al. investigated sperm chromatin integrity (by sperm chromatin structure assay) and quality of sperm chromatin condensation (by toluidine blue, aniline blue and chromomycin A3 staining) without finding any differences in the percentages of cells with defective chromatin in the overweight and obese patients compared with men with normal BMI [77].

Mitochondrial activity seems to be impaired in obese patients: in a study on 305 patients the obese group had a lower percentage of sperm with mitochondrial activity DAB class II (>50% of the midpiece was stained) and a higher percentage of DAB classes III and IV,(sperm with low or zero mitochondrial activity) [75]. In a study on 212 healthy men, aiming to identify which lifestyle factors were related to sperm aneuploidy, obesity was associated with an increase in the number of additional chromosome 21 as compared to normal weight men [78].

In a group of 107 male patients, who was referred to the fertility laboratory for diagnostic semen analysis or collection of a semen specimen for use for in vitro fertilization,

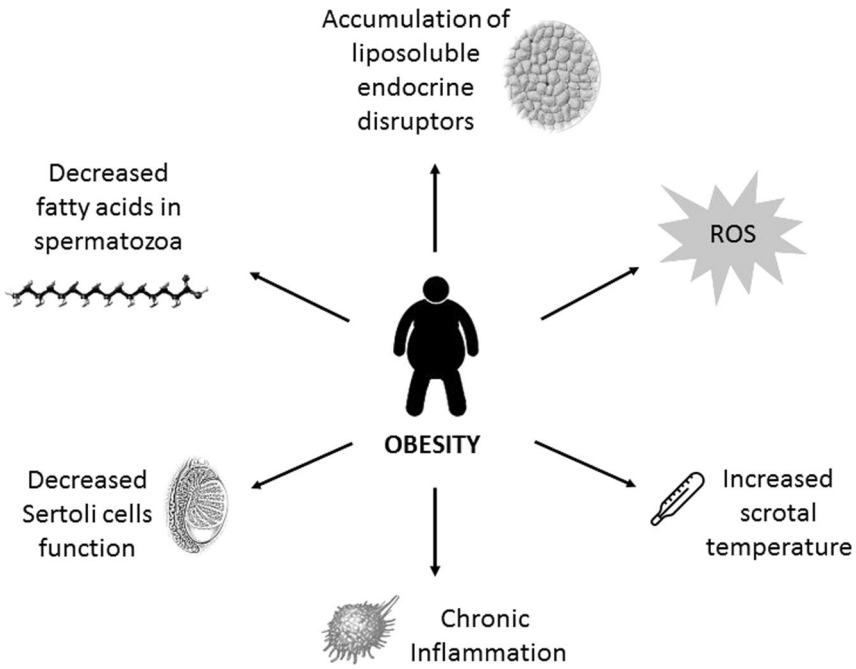

Fig. 2 Physiopathology of obesity-induced sperm alterations

BMI was inversely correlated with hyaluronan binding score. This score is an indicator of completion of normal spermatogenesis, which has been used to identify mature sperm with normal chromosome development and oocyte-binding capability [79].

Effect of male obesity on offspring health

In addition to the alteration in male fertility, obesity seems to affect also offspring health. In animal studies it has been demonstrated that paternal obesity and glucose intolerance could directly impact the metabolic syndrome susceptibility of the offspring [80]. In addition to the reported changes in metabolic profile in offspring, one study in a rodent model of male obesity has also reported a negative effect of male obesity on the reproductive health of male and female offspring extending to 2 generations [81]. Even if the exact mechanisms of these transgenerational effects of male obesity is not clearly understood, genetic association analyses suggest that the epigenome of multiple tissues is influenced by adiposity [82]. Hence, sperm cells may carry epigenetic changes, as methylation, which could be the underlying cause of the alteration of offspring health [83].

Obesity and in vitro fertilization (IVF) outcomes

Several studies analyzed the influence of male obesity on success following assisted reproductive technologies (ART). Most of the studies evaluated how men's BMI affects the outcomes of assisted fertilization. The study by Provost et al. that examined in a large number of IVF cases, the implantation rate, clinical pregnancy rate, live birth rate and pregnancy loss, demonstrated that obesity in men significantly impairs the clinical pregnancy rate (reduction from 45% in normal weight to 30% in patients with BMI > 50 Kg/m^2) and increase pregnancy loss (from 8.8 to 20% respectively in patients with normal BMI and in patients with BMI between 45–49.9) [84]. Another study including men with normal results from sperm tests showed an inverse association between BMI and live birth rate after ART [85]. Some differences have been found between in vitro fertilization and intracytoplasmic sperm injection (ICSI). The study by Keltz et al. showed a reduction of clinical pregnancy if the male partner was overweight after IVF but not after ICSI (odds ratio 0.21 vs 0.75 respectively) [86]. From our literature revision it seems that only one study concludes that the combination of an obese male and a normal-weight female is positively related to better implantation rates in IVF as well as ICSI cycles. The authors affirm that this combination is more likely to be found in couples with a higher social status [2].

Effects of weight loss on male fertility

Diet effects

Only a few studies have evaluated the effect on reproductive hormones of restricted energy intake (Table 1). An increase of androgen serum levels has been described after

Table 1 Summary of studies on the impact of weight loss through diet, in men with obesity: overall, weight loss through diet improves sex hormones levels, particularly androgens and sex hormone binding globulin, sometimes sexual function and rarely seminal parameters (semen volume and total sperm count)

Authors	TT	FT	E2	LH	FSH	SHBG	TYPE and duration of weight loss
Kaukua [87]	↑					↑	VLCD (4 months); no changes in sexual function
Khoo [88]	↑						LCD (8 weeks); improvement also in IIEF and IPSS
Khoo [89]	↑					↑	LCD and HP (8 and 52 weeks); improvement in IIEF, IPSS, FMD
Niskanen [90]	↑	↑				↑	VLCD (9 weeks) and maintenance period (12 months)
Stanik [113]	↑			↓			Weight reduction (8 and 20 weeks)
Strain [114]	↑	↑				↑	Weight reduction (5 and 39 months)
Hakonsen [93]	↑					↑	Weight reduction (14 months); improvement in AMH serum levels, semen volume and total sperm count
Reis [97]							No effect of exercise and diet for 4 months
Klibanski [92]	↑			↓	↓		Effect of fasting on sex hormones serum levels

TT total testosterone, *FT* free testosterone, *E2* oestradiol, *LH* luteinizing hormone, *FSH* follicle stimulating hormone, *SHBG* sex hormone binding globulin, *VLCD* very low calorie diet (800 kcal/day), *LCD* low calorie diet (900 kcal/day), *IIEF* international index of erectile function, *IPSS* international prostatic symptoms score, *FMD* brachial artery flow-mediated dilatation, *HP* high protein-low fat diet (reduction by 600 kcal/day), *AMH* anti müllerian hormone

weight-loss induced by LCD [87–90] and it has been sometimes associated with estrogen decrease, but these were not recent studies [91]. One study evaluated 38 obese men and divided them into two groups: one group of 19 subjects was treated with 12 weeks very low calorie-diet (VLCD), total energy intake of approximately 800 kcal/day) and subsequent 10 weeks behavioural variation, the other group of 19 untreated control subjects [87]. The rapid weight loss induced by VLCD resulted in increase of SHBG, testosterone, HDL-cholesterol and decrease of insulin and leptin serum levels, and these changes were maintained until the end of 8-month follow-up[87]; additionally, when the changes in metabolic and hormonal variables induced by maintained weight loss were evaluated in backward regression analysis, the decrease in insulin resistance was the most significantly related parameter to serum testosterone levels [87]. These data suggest a crucial role of increase of insulin-sensitivity in the restoration of the eugonadal status in obese men.

A strong correlation between insulin-sensitivity increase and testosterone levels has also been demonstrated by another study which has evaluated sex hormones serum levels, sexual function assessed through IIEF-5 score and low urinary trait symptoms (LUTS) assessed through IPSS-score in men with abdominal obesity with or without T2DM compared to a control group of men without diabetes but with similar body mass index and WC, before and after 8 week-low e diet (LCD), total energy intake of approximately 850–900 kcal/day) [88]. Weight loss significantly correlated with increase of insulin-sensitivity, total testosterone serum levels, IIEF-5 and sexual desire item (SDI) scores; moreover, IIEF-5 and SDI scores were positively associated with the magnitude of waist circumference reduction, reflecting visceral fat accumulation [88]. IPSS score was positively correlated with weight and abdominal adiposity loss and reciprocally associated with IIEF-5 and SDI score, suggesting that LUTS as well as sexual dysfunction in obese men might represent a feature of abdominal obesity, being improved by weight and waist circumference reduction [88]. These effects of diet-induced weight loss were confirmed in a cohort of 31 men with obesity and diabetes, who experienced an improvement of hormonal, sexual and urinary functions not only through an initial 8-week low-calorie diet but also through an alternative 8-week initial and then a 44 week maintenance high-protein, low-fat and reduced-carbohydrate diet (HP) program based on a reduction in daily intake of approximately 600 kcal/day [89]. Additionally, this study demonstrated a significant decrease of CRP and IL-6, which represent important inflammatory markers, and an improvement of endothelial function assessed through soluble E-selectin levels and brachial artery flow-mediated dilatation increase; [89] these further effects induced by diet-associated weight loss suggest other mechanisms potentially involved in the improvement of sexual and urinary function in obese men.

Finally, a study evaluated the effect of rapid weight loss obtained through 9-weeks VLCD and 12 month-sustained weight maintenance on sex hormones serum levels in a cohort of 58 men with abdominal obesity [90]. SHBG serum levels significantly increased during weight loss induced by VLCD and decreased during weight maintenance, remaining however higher than baseline levels; free testosterone significantly increased both during rapid weight loss induced by VLCD and at the last of weight maintenance 1 year-period, whereas total testosterone showed an intermediate trend between SHBG and free testosterone variations [90]. These findings emphasized the importance of weight loss in the prevention of progressive

Table 2 Summary of studies on the impact of bariatric surgery on sex hormones and sexuality, in men with obesity: bariatric surgery improves sex hormones levels, particularly, androgens, but also estrogens, gonadotropins and sex hormone binding globulin

Authors	TT	FT	E2	LH	FSH	SHBG	Notes
Botella- Carretero [95]	↑	↑				↑	Increase of FT strongly associated with reduction in IR
Aarts [98]	↑	↑					FT as a possible marker of hypogonadism in men with obesity
Alagna [96]	↑	↑	↓	↑	↑		
Bastounis [103]	↑		↓		↑	↑	
Hammoud [101]	↑	↑	↓				Increase of sex hormones correlates with increase in sexual function
Reis [97]	↑	↑	↓		↑		24 months after bariatric surgery, also increase in sexual function
Rosenblatt [104]	↑	↑				↑	6 years after bariatric surgery, no association with increase in sexual function
Samavat [106]	↑	↑	↓			↑	>WC at baseline in severe hypogonadism is associated with >reduction of WC after surgery
Calderon [94]	↑	↑				↑	FT strongly associated with reduction in IR; no differences between surg. Gastric bypass and restrictive technique
Pellittero [105]	↑	↑	↓		↑	↑	12 months after bariatric surgery; increase in inhibin B and AMH, also in case of decrease at baseline

TT total testosterone, *FT* free testosterone, *E2* oestradiol, *LH* luteinizing hormone, *FSH* follicle stimulating hormone, *SHBG* sex hormone binding globulin, *IR* insulin-resistance, *WC* waist circumference, *AMH* anti müllerian hormone

hormonal imbalance associated with obesity and highlighted the crucial role of lifestyle modifications as first-line treatment of male hypogonadism secondary to obesity [90].

Only one anecdotal study reported a negative effect of diet on sex hormones serum levels, describing a combined decrease of FSH, LH and testosterone after fasting in obese men [92]; this could be explained by the excessive and probably detrimental effects of fasting and fasting-associated ketosis on metabolism and sex hormones [91].

The effects on semen quality of weight loss obtained through non-surgical interventions have been poorly studied. One study evaluated 43 men with obesity before and 14 weeks after a weight loss program based on healthy diet and physical exercise [93]. Weight loss was significantly associated with an increase in total sperm count, semen volume, total testosterone, AMH and SHBG serum levels; moreover, the group of men with obesity with the largest weight loss showed a significant increase in total sperm count and normal sperm morphology [93]. The results of this study suggested that weight loss induced by non-surgical interventions could improve semen quality of men with obesity, even if further studies with a larger cohort and a longer follow-up period are needed to establish if this effect is really induced by weight loss per se or by a direct contribution of general lifestyle modification [93].

Bariatric surgery effects

Several studies have analysed the impact of bariatric surgery on sex hormones in men with obesity, by demonstrating, overall, a positive effect of weight loss induced by bariatric surgical intervention on sex hormones serum levels (Table 2).

Several studies have demonstrated an increase of total testosterone serum levels after weight loss obtained through bariatric surgery, and the improvement in total testosterone serum levels was inversely correlated with fasting glucose and insulin serum levels, confirming that insulin-sensitivity and androgen serum levels might be positively associated [94, 95]. Moreover, the increase in total testosterone levels was negatively associated with hyperestrogenism and leptin serum levels, therefore confirming their role of crucial disruptors of HPG axis in men with obesity [94, 96]. Lastly, the improvement of testosterone serum levels was found to be associated with waist circumference reduction [97]. The association between hypogonadism and visceral obesity has been extensively investigated. A remarkable prospective study evaluating a cohort of 55 men with obesity undergoing bariatric surgery, which included 29 affected by hypogonadism and 26 who were eugonadal, demonstrated that total testosterone serum levels were increased after bariatric surgery, in both hypogonadal and eugonadal groups, and that the increase in total testosterone serum levels was strongly correlated to the reduction of waist circumference in hypogonadal patients [97]. Moreover, a longitudinal assessment of results showed that hypogonadal patients with obesity had a higher waist circumference at baseline, and a larger waist circumference reduction after bariatric surgery, compared to men who were eugonadal [97]; the results of the study suggested that hypogonadism might have a possible role of predictor of waist circumference reduction after surgical intervention [97]. Total testosterone increase has often been associated with the increase in calculated free testosterone, assessed with Vermeulen formula [95, 97], and, in turn, free testosterone increase has been correlated with fasting glucose [94] and

improvement in insulin-resistance, assessed with the HOMA-index [95]. Considering that total testosterone decrease is often associated to SHBG serum levels reduction in men with obesity, one study highlighted that free testosterone might be a better diagnostic marker for hypogonadism, aimed at preventing overestimation of this condition in obesity [98]. In line with this assumption, several studies have demonstrated a significant increase of SHBG serum levels after weight loss obtained through bariatric surgery [95, 99], and found a negative correlation between SHBG, insulin-resistance and visceral adiposity and hepatic fat [90, 100], confirming the crucial link in men with obesity between insulin-resistance improvement and restoration of eugonadal status [97].

Sexual and erectile function have been frequently correlated to androgenic status, and an overall improvement in sexual function has been reported after weight loss obtained through bariatric surgery [101, 102], probably due to recovery from hypogonadal status [103], amelioration of obesity comorbidities, such as metabolic syndrome and hypertension, known as erectile dysfunction organic promoters [101], and improvement of psychological profile after weight loss. Conversely, one study reported no improvement of sexual function after bariatric surgery, pinpointing the residual overweight and the persistence of obesity comorbidities as leading causes of unchanged sexual function [104].

A significant decrease of estrogen serum levels has been consistently observed in men with obesity, after bariatric surgery [96, 99, 105, 106], and has been found to be mainly induced by the reduction of adipose tissue-associated aromatase activity, which is responsible of hyperestrogenism in these men [96, 99, 105]. The reduction of estrogen serum levels induced by bariatric surgery determines the suppression of estrogen-mediated negative feedback on the HPG axis, as demonstrated by LH [96, 106] and FSH [96, 99, 105, 106] increase and contributes to the restoration of eugonadal status after bariatric surgery-induced weight loss [95, 96, 99, 105]. Hyperestrogenism in men with obesity has been interestingly correlated with down-regulation of GLUT4 (glucose transporter-4), a molecular target mediating peripheral insulin-sensitivity [94], therefore suggesting that hyperestrogenism might be involved in increased insulin-resistance in these men, and that the decrease in estrogen serum levels induced by bariatric surgery might contribute to improve insulin-sensitivity [94].

There is little evidence about the effects of bariatric surgery on AMH and inhibin B serum levels. One study evaluated a cohort of 33 men prior to and 12 months after bariatric surgery, by assessing serum levels of FSH, LH, total and free testosterone, SHBG, prolactin, estradiol, AMH and inhibin B; the results of the study demonstrated a significant improvement in FSH, total and free testosterone, SHBG, prolactin and estradiol serum levels after bariatric surgery [105]. At baseline, AMH and inhibin B serum levels were lower in hypogonadal, compared to eugonadal patients; after bariatric surgery, both AMH and inhibin B serum levels were not significantly changed, although inhibin B showed a trend to an improvement, and a negative correlation with BMI [105]. Moreover, in those cases showing a lower-than-normal serum level of both AMH and inhibin B at baseline, a complete normalization of the two hormones was observed after bariatric surgery, suggesting that weight loss induced by bariatric surgery might restore normal AMH and inhibin B serum levels [105, 107]; however, few studies addressed this hormonal effect, and further investigations concerning variations in AMH and inhibin B levels after bariatric surgery are needed, in order to better define whether Sertoli cell dysfunction occurs in men with obesity, and whether weight loss induced by bariatric surgery might exert beneficial effects.

Lastly, bariatric restrictive interventions, such as sleeve gastrectomy, and bariatric gastric bypass interventions, did not significantly differ in regard to their impact on sex hormones serum levels [94]. Furthermore, the impact of bariatric surgery on sex hormones was more significant than that of weight loss diet programs, probably due to less pronounced and less durable weight loss obtained through non-surgical interventions, compared to that achieved by bariatric surgery interventions [108].

Despite several studies having demonstrated the impact of bariatric surgery on hormonal profile, the effect of massive weight loss induced by bariatric surgery on seminal parameters is still unclear. Some anecdotal case reports highlighted the existence of a negative effect of bariatric surgery on semen quality, probably associated with malabsorptive complications of bariatric surgery [109–111]. Cases of azoospermia with spermatozoa maturation arrest were described in a study evaluating six men after surgical intervention by Roux-en-y gastro-intestinal bypass [109], two cases of impaired semen quality have been reported twelve and eighteen months after bariatric surgery, combined with a subsequent decrease of ART outcome [110], and three case reports have described a negative impact of bariatric surgery on seminal parameters, although two of these reports described a successful pregnancy obtained through ICSI in obese subjects [111].

A 24 months-prospective, randomized, and controlled study on 20 men with obesity who underwent a four-month lifestyle modification followed by surgical intervention of gastric bypass, matched to men with obesity in clinical follow-up, investigated the relationship between semen quality and surgery-induced weight loss [102]; the results of the study highlighted that bariatric surgery had no significant impact on semen quality, although this lack of an effect might be explained by the small number of patients

enrolled in the study [102]. Conversely, two recent prospective interventional studies have demonstrated a positive impact of bariatric surgery on semen quality [106, 112]. In one study, semen quality and sex hormones levels were evaluated in a cohort of 46 men prior to and twelve months after sleeve gastrectomy [112]. Patients were divided into 3 groups on the basis of their different seminal profile at baseline, azoospermia was detected in 13 patients (28.3%), oligozoospermia in 19 patients (41.3%), and normal sperm concentration in 14 patients (30.4%); twelve months after bariatric surgery, serum total testosterone increased in all groups, whereas an improvement in sperm concentration was observed only in azoospermic and oligospermic patients, with sperm retrieval in 6 out of 13 patients (46%) who initially had azoospermia [112]. Sperm motility and normal morphology did not significantly change after surgery, although a trend towards improvement was reported; similarly, no significant differences were reported in other sex hormones levels [112]. The results of this study suggest that bariatric surgery might be more effective in improving semen parameters in men with obesity with a worse semen quality at baseline, although a limitation of the study included the lack of an assessment of sperm DNA integrity alteration a possible pathophysiologic mechanism of infertility in men with obesity [112]. In line with this evidence, another recent two-armed prospective study evaluated 31 men with morbid obesity undergoing laparoscopic gastric bypass ($n = 23$), or in clinical follow-up ($n = 8$), by assessing sex hormones serum levels, conventional (sperm count, motility, and morphology and semen volume), and unconventional (sperm DNA fragmentation and IL8 seminal levels) semen parameters, at baseline, and 6 months after bariatric surgery or patients recruitment [106]. The results demonstrated a significant improvement of sex hormones serum levels (FSH, LH, total testosterone, SHBG, calculated free testosterone, and estradiol), semen volume and sperm viability, after bariatric surgery, compared to control group [106]; moreover, a trend towards an improvement of sperm motility total sperm count, IL8 seminal levels and sperm DNA fragmentation as well as a trend towards an increased prevalence of normozoospermia, were described [106]. The improvement of seminal parameters was strongly correlated with BMI decrease, which represented the most influencing factor on seminal variations in univariate and multivariate analysis [106]. The results of this study suggest that changes in seminal parameters after bariatric surgery are less pronounced, compared to changes in sex hormones levels, and could be mediated by both post-testicular mechanisms, as suggested by the decrease of IL8 seminal levels and sperm DNA fragmentation, which can be interpreted as markers of post-testicular inflammation, and testicular mechanisms, which however still remain unclear [106, 107].

Conclusions

The current review provides an overview of the mechanisms impairing sex hormones and seminal quality in men with obesity and discusses the reversibility of these effects through non-surgical and surgical weight-loss programs.

Male secondary hypogonadism is identified as one of the most relevant hormonal complications of obesity; this endocrine disorder can be induced by the complex interplay of multiple central, peripheral and testicular factors, which alter the normal function of HPG axis at different levels. Impaired spermatogenesis represents another relevant obesity-related andrological complication. Several preclinical studies in animal models have recognized the existence of a negative correlation between obesity and semen quality, probably due to increased seminal oxidative stress, sperm DNA integrity disruption, and increased local release of inflammatory mediators within the reproductive tract [48–53, 55–57]. Moreover, a decrease of pregnancy rate after ART has been demonstrated in obese men [84–86]. The evidence gathered by the current review demonstrates a positive impact of weight loss in men with obesity on both sex hormones serum levels and semen quality. LCD significantly improves sex hormones serum levels [87–90, 93, 113, 114], and, less consistently, sexual function [88, 89], whereas weak evidence exists about LCD-induced improvement of semen parameters in obese men [93]. Weight loss after bariatric surgery, overall, is more significant and durable than LCD-induced weight loss; this is probably the cause of the greater improvement of both sex hormones serum levels and semen quality, in men with obesity undergoing bariatric surgery [108]. Several mechanisms have been found to be involved in the improvement of hormonal profile and seminal parameters, after weight loss [104]. Visceral fat reduction and the consequent increase of insulin-sensitivity [104, 111, 112], as well as the reduction of hyperestrogenism negative feedback on the HPG axis, and the decrease of leptin serum levels [106, 114] have been all recognized as major mechanisms of androgen increase after weight loss. On the other hand, the mechanisms involved in the improvement of seminal parameters after weight loss still remain unclear. Both testicular and post-testicular factors (reduction of scrotal temperature and reduction of seminal accessory glands inflammation and inflammation-correlated oxidative stress) have been hypothesized as possible mediators of the positive impact of weight loss on semen quality [106, 107, 112].

Nevertheless, further preclinical and clinical studies are needed to better define the entity of fertility impairment in men with obesity, and to identify the underlying pathophysiological mechanisms. Moreover, further randomized and controlled clinical trials are mandatory to adequately

estimate the clinical benefits of weight loss by both LCD and bariatric surgery on male fertility.

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