Expert Reviews

The impact of obesity on male reproduction: its biological significance

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Ana Carolina Martini*[1], Rosa Isabel Molina[2], Andrea Tissera[2], Rubén Daniel Ruiz[1] and Marta Fiol de Cuneo[1]

[1]*Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET). Cátedra de Fisiología Humana, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba. Santa Rosa 1085, X5000ESU, Córdoba, Argentina*
[2]*Laboratorio de Andrología y Reproducción (LAR). Chacabuco 1123 PB, 5000, Córdoba, Argentina*
**Author for correspondence:*
Tel.: +53 351 433 2019
Fax: +53 351 433 2019
acmartini2000@yahoo.com

Since obesity and male subfertility have increased in parallel during the last decades, the hypothesis of an association between these two phenomena has been explored by several researchers. Although there is no consensus apparently obesity impacts men's reproductive potential by several mechanisms, like alterations on the hypothalamus–pituitary–testicular axis, modifications of spermatogenesis and semen quality and/or impairment of men's sexual health. This review intends to summarize the underlying bases of such alterations and propose new ones, without miscalculating their biological significance. Obesity is not rigorously related to subfertility; in addition, the existence of a genetic predisposition to obesity-linked sterility is currently under investigation. Nonetheless, the impact of obesity on male reproductive potential must be fully elucidated since the prevalence of obesity is increasing and consequently, the number of obese men with reduced fertility will rise as well.

Keywords: epididymal maturation • epididymis • hypothalamic–pituitary–testicular axis • leptin • male fertility • obesity • overweight • semen quality • spermatogenesis • spermatozoa

Twenty years ago, Carlsen *et al.* published a manuscript that stunned scientists and physicians [1]. In their meta-analysis 'Evidence for decreasing quality of semen during the past 50 years', which included almost 15,000 healthy men, the authors found a 50% decline in seminal sperm density between 1940 and 1990 (113×10^6/ml vs 66×10^6/ml, respectively). Additionally, they found a significant decrease of seminal volume, which indicated an even more pronounced decrease in total sperm count. As expected, this publication opened a heated debate. During the following years, numerous studies have confirmed a decline in human seminal quality [2,3] which motivated the study of its possible etiological mechanisms.

Somewhat in parallel with this semen impairment, the proportion of overweight and obese men (and women) has dramatically augmented during the last decades [3,4]. At this moment, obesity is being considered as a pandemic disease [5]. For this reason, it was only a matter of time that these two phenomena were associated as a theoretical cause–effect fact. Finally, in 2004, Jensen *et al.* published probably the most renowned study attributing a detrimental effect on male sperm count and reproductive hormonal profile to overweight and obesity [6]. In their publication, which included more than 1500 young Danish men subjected to a compulsory physical examination for the military service, the authors found that serum testosterone (T), sex hormone binding globulin (SHBG) and inhibin B significantly decreased when the BMI increased, whereas free androgen index and estradiol (E_2) augmented. Moreover, they also reported that men with BMI >25 kg/m^2 (overweight or obese) had a significant reduction in sperm concentration and total sperm count when compared with men classified as 'normal'.

Between Jensen's publications and today's publication, a vast number of studies have intended to confirm or discard the hypothesis of obesity as etiological factor for male fertility decline [4–9]. Nevertheless, there is still no consensus about the degree of the damage provoked by overweight on male reproductive function; differences in the selected populations may be responsible for these disagreements. Certainly, there are several issues to consider when comparing the studies, like size and reproductive status of the studied population (proven fertile males or patients attending an andrology center); degree of obesity consider; if the study

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took into consideration or not other anthropomorphic parameters further than BMI, such as waist circumference (which correlates better with the reproductive hormonal profile) [4]; if possible confounding factors were taken into consideration since several social habits may influence sperm quality even more than body weight (smoking, drinking or contents of the diet) [10] and the biological importance of the seminal damage provoked by obesity, since a significant but mild diminution in sperm parameters may have differential relevance on the fertility status of subfertile or healthy volunteers.

In line with the above-mentioned thoughts, the objectives of this review were to summarize what the authors actually know about the association between obesity and male reproductive function and to analyze the biological significance of this association.

The dilemma of obesity

According to data provided by the WHO in 2010, in North America, Australia and several countries of Europe and South America, the prevalence of overweight and obesity is higher than 65% [101]. Actually, in the USA, more than 35% of the adult population suffers of obesity. In 1999–2000, 27.5% of men were obese and these percentages increased up to 35.5% by 2009–2010 (37.5 millions of men). Furthermore, in 1999–2000, the prevalence of obesity was higher in women than in men, but by 2009–2010, the prevalence of obesity by gender was virtually equal [11]. It is intriguing; nonetheless, that this rise in the incidence of obesity is not restricted to industrialized societies, but has also become a health problem in developing countries [101]. Indeed, nowadays the world's overweight population is higher than its underweight population [102].

The most widespread measurement to quantify overweight and obesity is BMI, which is the ratio between a person's weight (in kilograms) and the square of his/her height (in meters) [4,101]. The WHO considers that the people with BMI greater than or equal to 25 kg/m^2 are overweight and those with BMI greater than or equal to 30 kg/m^2 are obese [101]. Nevertheless, there are other methods to estimate the excess of fat mass, like waist circumference and waist/hip ratio [4]. In fact, it has been suggested that these may be even better markers for overweight and obesity than BMI [4,5,7]. However, few studies have evaluated such alternative measurements of obesity.

Furthermore, a recent study has demonstrated that the consumption of some types of feeds (like cereals) correlates with sperm quality yielding coefficients greater than BMI [10]. Likewise, it has been published that the diet composition may modify SHBG levels, being proteins and fibers but not fat or carbohydrates the most important factors [12].

In summary, although BMI may not be the best/unique system to quantify overweight and obesity, these are serious health problems worldwide. Since an important proportion of men in reproductive age are obese [13] and males alone are responsible for approximately 25–30% of all the cases of subfertility (plus 30% in combination to female factors) [14], the possible association between obesity and male fertility should be analyzed.

Impact of obesity on the hypothalamus-pituitary-testicular axis physiology

Hormonal profiles of normal & obese men

In healthy adult males, the medial basal region of the hypothalamus secretes gonadotrophin-releasing-hormone (GnRH) in a pulsatile manner. This GnRH interacts with specific pituitary cells, stimulating the synthesis and release of gonadotrophins: lutheinizing hormone (LH) and follicle-stimulating hormone (FSH). The LH acts on Leydig cells stimulating T secretion, which in turn inhibits the release of GnRH and LH via negative feedback [9]. Testosterone (T) circulates in plasma as free (or unbound), albumin-bound and approximately 44% bound to SHBG [9,15]. The proportion of free T, together with the albumin-bound fraction is considered as the bioavailable T, and correlates better with clinical symptoms than total T [9,16]. The serum fraction of SHBG-bound T is proportional to the SHBG level. Besides, SHBG production in the liver is regulated by a number of hormones (like E_2, thyroid hormone and insulin) and medical conditions (like hypothyroidism and insulin resistance) [9]. In addition, in normal circumstances, a small proportion of circulating T is converted to E_2 by the action of the enzyme P450 cytochrome aromatase. This enzyme is present only in a few tissues; the highest levels are found in adipose cells [7,9,17].

FSH does not play a major role in the control of T secretion; instead, it participates via Sertoli cells in testicular gametogenesis. Sertoli cells provide developing germ cells with structural and hormonal support. That is the reason why the number of such cells in adult's testis determines gonads size and daily sperm production, since each Sertoli cell can only support/nourish a fixed number of germ cells [18]. Sertoli cells secrete also peptidic hormones, mainly inhibin B. This substance is a heterodimeric glycoprotein that shows a diurnal rhythm (in parallel to T) which, in turn, inhibits FSH production via negative feedback [9]. Since circulating levels of inhibin B highly correlate with the number of Sertoli cells, this hormone is considered a marker of spermatogenesis [19,20].

Although there is no total consensus about this point, the hormonal profile of obese male seems to be quite different (Figure 1). It is usually characterized by a decrease in total and free T levels, decreased gonadotrophins concentrations and increased circulating estrogen levels. Furthermore, SHBG is usually reduced in obese males, phenomenon that attenuates the significance of low total T levels but magnifies estrogens importance [4–9]. Nevertheless, although there is a physio-pathological reason for each one of the above-mentioned hormonal changes, the truth is that not all obese males have reproductive hormonal levels outside the normal range [9].

Which are the bases of this altered hormonal profile? There is an inverse association between plasma total T, free T and SHBG with BMI or visceral fat [21]. One of the reasons is that visceral fat is associated with elevated concentrations of insulin, C-peptide and glucose intolerance [22] and insulin is thought to be the cause of reduced SHBG levels in obese patients, since it alters the liver synthesis of the globulins [23,24] (see 'Role of leptin and other adipose-derived substances'). Nevertheless, the reduced concentrations of T found in obese men are apparently independent of SHBG

decrease, suggesting a failure at the reproductive axis [25]. Generally, in obese males, LH pulsatility remains undisturbed, but there may be an attenuation in the amplitude of these pulses [26], which may alter T secretion. Nonetheless, the decrease in LH levels or LH pulse amplitude depends on the degree of obesity, being observed mainly in extremely obese men [27].

Another possibility, but not exclusive, is that the common increase in plasma leptin (L) levels that characterizes obesity exerts deleterious effects on hypothalamus-pituitary-testicular (HPT) axis [28]; in addition, there is evidence that L may act directly on the testis [29,30] [Figure 1.].

It has also been demonstrated that sleep apnea, a syndrome of higher incidence among obese men, has a negative impact in T plasma concentration, since it disrupts the LH nightly peak [31,32]. As a result, the obesity-related hypogonadism, when present, may be the consequence of multiple factors.

Finally, the rise in the circulating levels of E_2 found in obese men is explained by the increased aromatization of plasma T due to the elevated number in the amount and size of the adiposites [4–9]. This results in a decrease of the T to E_2 ratio, that leads to further abdominal fat deposition [17] and a more pronounced negative feedback on the HPT axis [33], with the consequent alteration in the GnRH pulses, in the secretion of gonadotrophins and in the circulating levels of T [8,34,35]. It is important to remember that E_2 has a higher negative feedback capacity than T [1,36].

In humans, an association between decreased T/E2 ratio and severe male infertility has been demonstrated [37]. Also, studies in experimental animals have showed that the daily administration of high doses of estrogens to male rats diminishes sperm production and the weight of the testis, epididymis and seminal vesicles in a dose-dependent manner [38]. However, as Hammoud *et al.* pointed out, it is doubtful that mild augments in circulating E_2 are sufficient to notably alter intratesticular estrogen concentrations [8]. In later work, the same authors reported that in obese male, an aromatase enzyme polymorphism modulates the relation between weight and circulating E_2 levels [39]. This may explain the reason why only certain obese men experience this rise in E_2 and subsequent fertility problems, whereas others experience no fertility impairment [4].

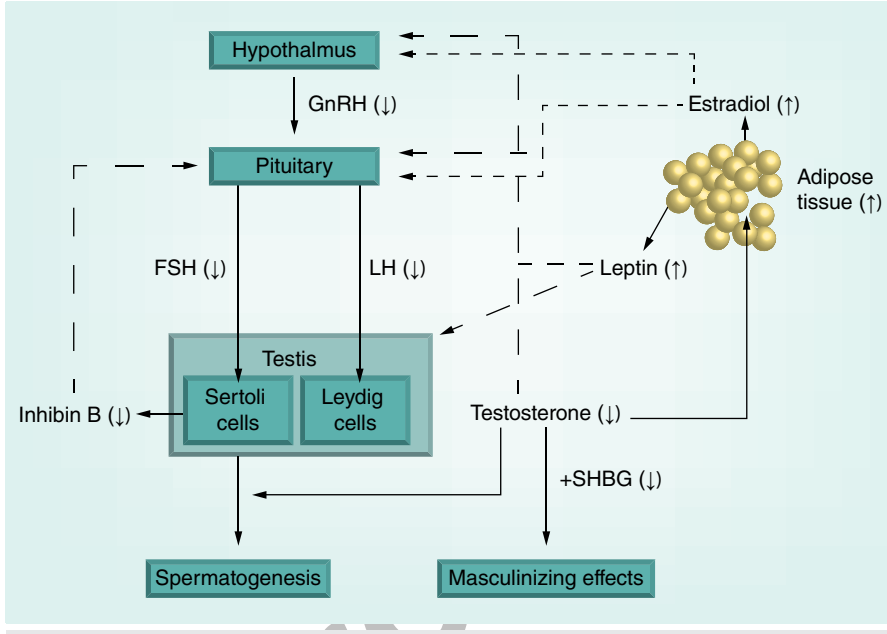

Figure 1. Physiology of the hypothalamus-pituitary-testicular (HTP) axis of a healthy adult man and possible modifications exerted by obesity (in parenthesis). The hypothalamus secretes GnRH in a pulsatile manner, which interacts with the pituitary, stimulating the synthesis and release of gonadotrophins: LH and FSH. FSH participates, via Sertoli cells, in testicular gametogenesis and stimulates inhibin B secretion. This peptidic hormone may be diminished in obese men, although the biological bases of this change are not fully understood. The LH acts on testicular Leydig cells stimulating testosterone secretion, which in turn inhibits GnRH and LH release via negative feedback. Testosterone circulates in plasma as bioavailable or bound to SHBG, which synthesis may be decreased in obese men. Additionally, in normal circumstances, a small proportion of circulating testosterone is converted to estradiol by the action of the adipose enzyme P450 cytochrome aromatase. In obese men, the augmentation of adipose tissue may increase aromatization of plasma testosterone, which results in an enhance of plasma estradiol with the consequent alteration in the GnRH pulses, the secretion of gonadotrophins and in the circulating levels of testosterone. Finally, the increase in plasma leptin concentrations typical of obesity may exert deleterious/inhibitory effects on HPT axis, as well as a direct negative impact on testis physiology. Entire arrows: stimulating or positive effects; interrupted arrows: inhibitory or negative effects (there are no differences between dotted and dashed arrows).
FSH: Follicle-stimulating hormone; GnRH: Gonadotrophin-releasing-hormone; LH: Lutheinizing hormone; HPT: Hypothalamus-pituitary-testicular; SHGB: Sex hormones binding globulin

Role of leptin & other adipose-derived substances

Besides its central role in energy homeostasis, white adipose tissue is a major secretory and endocrine organ that segregates around 30 biologically active proteins. These substances can be grouped as either adipose-derived-hormones (L, adiponectin, resistin and others) or adipokines, which are immunomodulating agents, such as TNF-α, IL-6, plasminogen activator inhibitor-1 and tissue factor [4,28].

Leptin is a 16 kDa protein; its plasma concentration is directly related to the amount of adipose cells [28]. Although normal levels of L are required for overall reproductive health, an excess of this protein may importantly contribute to hypogonadism and abnormal spermatogenesis in obese men [5,7,23,35]. In an *in vitro* murine model, it has been determined that L concentrations similar to those observed in obese males significantly reduce the T synthesis stimulated by human chorionic gonadotrophin, by the inhibition of the conversion from 17OH-progesterone to T [40]. Furthermore, Isidori *et al.* found that circulating L correlates with T levels even after controlling for SHBG, LH or E_2 concentrations

and that L was the best hormonal predictor of lower androgen levels in obese men [23]. Besides, since not only the spermatocytes but also the mature sperm express the L receptor, it is supposed that this substance may affect not only spermatogenesis but also seminal sperm quality independently of its effects on HPT axes [23,29,41]. At this respect, Ishikawa *et al.* have reported a significant association between plasma L concentrations and spermatogenic dysfunction [30].

Other adipose-derived-hormone that has been related to alterations of the hormonal profile in obese men is resistin. This hormone induces insulin resistance, with the consequent plasma insulin increase and Type 2 diabetes [28,42]. As previously mentioned, hyperinsulinemia is able to inhibit liver SHBG secretion [24]. Several studies have demonstrated that SHBG and total T levels are inversely correlated with those of insulin, even after adjusting for BMI (reviewed in [43]). Moreover, the results from a diabetes management center indicate that hypogonadism is present in 33% of men with noninsulin-dependent diabetes mellitus [44]. Inversely, in a placebo-controlled study, the intramuscular administration of T to hypogonadal males with Type II diabetes, exerted beneficial effects on glycemic control, insulin resistance, total cholesterol and visceral adiposity [45]. These results support a bi-directional link between glucose metabolism (and related pathologies like diabetes or metabolic syndrome) and total/visceral adiposity with testicular steroidogenic function.

The significance of inhibin B

Another hormone that is frequently altered in obese men is inhibin B [8,46–48]. Winters *et al.* have demonstrated that inhibin B levels decrease whereas BMI rise, suggesting a direct role of obesity on the suppression of the function of the Sertoli cells and spermatogenesis [47]. Other studies also support this hypothesis [19,20]. However, it is not clear yet if these diminished levels of inhibin are attributable to the negative feedback on FSH exerted by hyperestrogenemia, since the increased estrogen levels associated with obesity are not as pronounced as the diminution of inhibin B [8,47]. On the other hand, there is not a strong correlation between relatively small reductions of FSH and the more dramatic diminution of inhibin B [6,8,46,47]. Some authors have postulated that hyperinsulinemia associated with obesity may be a possible explanation [8]. Anyway, it would be helpful to investigate the potential relationship between the direct effects of L on testis and inhibin B levels. Zorn *et al.* studied 210 male partners from infertile couples that after adjusting for BMI they showed a negative correlation between L and inhibin B [48]. Whether this is a causal association or only a correlation, it remains to be established.

Effects of obesity on fertility & seminal quality

Several studies performed not only in couples seeking fertility treatment but also at epidemiological level, have explored the association between obesity and fertility. Some of them, but not all, have shown a significant association between elevated BMI and subfertility [49–51].

Searching the etiological bases of this subfertility, several studies have explored the link between BMI and semen quality, especially after Jensen's publication. In this study, the authors report a 21.6 and 23.9% significant reduction in sperm concentration and total sperm count, respectively, in men with BMI >25 compared with those classified as normal [6]. It is important to remark, nevertheless, that these overweight/obese men with reduced sperm density had a median sperm concentration of 39% (vs 46% in the normal group), which is considered normal by WHO [52]. Likewise, in a study among Australian fertile men, it has been proven that obese men had a significantly lower total sperm count than those with BMI <30 (324 vs 231 million) [53]. Moreover, in their meta-analyses, Sermondade *et al.* found that obese men had higher risks of oligozoospermia or azoospermia than normal ones [54]. Some other authors corroborated this negative association between obesity and sperm density [10,36,55]. On the contrary, MacDonald *et al.* published a meta-analysis in 2010, in which they did not find evidence of an association between BMI and sperm concentration or total sperm count [56]. In the same way, in a previous study performed in 794 men attending our andrology clinic, we did not find any significant association between BMI and sperm concentration or total sperm count [55]. Nevertheless, it is important to comment that nine of these patients had BMI >40; these morbidly obese men had a significant/important reduction in sperm concentration and seminal volume (sperm density: 18.0 ± 3.2, n = 9 in men with BMI ≥40 vs 43.6 ± 5.8, n = 146 in men with 30 ≤ BMI < 40, p<0.0052; seminal volume: 2.7 ± 0.4, n = 9 in men with BMI ≥40 vs 3.2 ± 0.2, n = 146 in men with 30 ≤ BMI < 40, p > 0.05) (unpublished results). Although the small sample of morbidly obese men did not allow us to make scientific valuable conclusions, these results support the idea that the degree of damage on sperm quality (and may be on other male reproductive features) depends on the degree of obesity. We are currently developing new investigations to elucidate these aspects.

On the other hand, in our study we found an inverse and significant association between BMI and total or rapid sperm motility [55]. Moreover, in the nine morbidly obese patients we found a significant increase in the percentage of nonmotile spermatozoa (45.7 ± 5.5, n = 9 in men with BMI ≥40 vs 33.3 ± 1.5, n = 146 in men with 30 ≤ BMI <40, p < 0.0244). The results regarding a negative association between obesity and sperm motility are in agreement with those of other authors [10,36,54] and in contraposition to others [6,20,53]. Qin *et al.* demonstrated, in a study performed in 990 fertile men, an inverse significant relation between BMI and sperm motility [57]. Similarly, Hammoud *et al.* reported that among 500 men attending an andrology laboratory, those that were obese had a significantly higher incidence of astenozoospermia [36]. Regretfully, none of these studies evaluated the seminal values of neutral α-glucosidase (NAG).

This substance is an enzyme secreted by the epididymal cells that modulates the maturation process of spermatozoa during their passage through the epididymis; motility acquisition is one of its characteristics [58–60]. Interestingly, in our study we found a very high (r = -0.99) and significant inverse association between BMI and seminal NAG levels [55]. Bearing in mind the known

androgen-dependency of NAG secretion [58,61] and the plasma T alterations reported in some obese patients, the motility profiles and the NAG levels found in our study support a possible deleterious effect of obesity on epididymal function. Another study previously performed in our laboratory has also linked the physiology of epididymis and NAG secretion with nutritional alterations [62].

Regarding the connection between sperm morphology and obesity, even employing different normality criteria, neither our study nor others have found alterations linked to body weight in this parameter [6,10,20,55]. In fact, there is a study in which the authors inform a positive association between BMI and the percentage of morphologically normal sperm [57]. On the other hand, a detrimental effect of obesity on sperm DNA fragmentation has been notified [63].

It could be assumed that all the hormonal alterations exposed in the first section of this review may be responsible for the obesity-linked subfertility or for the reduction in spermatozoa quality, but the truth is that some studies inform about deleterious effects on sperm attributable to obesity, which are independent of the volunteers hormonal profile [57] or inversely, hormonal alterations without sperm subquality [20,56]. Concordantly, in our study we were unable to find any differences in seminal T concentration between normal and obese patients [55]. Therefore, the sperm quality from obese patients must be analyzed separately (but not excluded) from their hormonal profile.

In summary, an important number of studies have confirmed a deleterious effect of obesity on spermatogenesis. Nevertheless, it is important to keep in mind that in general, the degree of such alteration is mild, remaining sperm parameters within normality limits. For the same reason, the authors usually inform the associations between BMI and sperm quality or trends, rather than significant differences in sperm parameters between obese and normal men. Furthermore, the effects of obesity are not consistent; which means that an important number of obese men remain normospermic [5,8]. These are the reasons why some authors propose that obesity enhances a predisposition to subfertility rather than cause it [5]. In such a way, there are some genetic diseases that present obesity and infertility simultaneously, such as Klinefelter [64] or Prader Willi syndrome [65].

Other factors linked to obesity that may alter men's reproductive ability

Obesity & sexual dysfunction

Many obese men face physical problems that could be partially responsible for their subfecundity; one of them is erectile dysfunction (ED). Bacon *et al.* examined age-specific prevalence of ED and informed that men with BMI >28.7 had a 1.3-times higher risk of presenting ED in comparison with men with BMI <23.2 [66]. Furthermore, in an American study published in year 2000, the authors reported that among men with symptoms of ED, 79% had BMI ≥28 [67]. Some other studies have corroborated an association between obesity and metabolic syndrome with ED [68–70], whereas others have failed to find a significant correlation [71]. In any case, two pathophysiological bases may explain obesity-linked ED. The first one is the small amount of T bioavailable levels previously described [68–70], the second one is the higher incidence of Type 2 diabetes and metabolic syndrome among the obese population [72]. The apparent connection is that visceral obesity increases proinflammatory factors thereby promoting inflammation and contributing to endothelial dysfunction [72]. Any factor that affects endothelial physiology, nitric oxide release or the integrity of the vascular bed will certainly contribute to ED, since erection depends on hemodynamics and vascular health [4,73]. Conversely, it has been demonstrated that diabetes control and weight loss improve erectile function [74].

Obesity is also associated with other cardiovascular risk factors such as smoking, hypertension and dyslipidemia, which have a strong epidemiologic independent link to ED [8,67,75]. Finally, it is important to keep in mind that obese men may have lower self-esteem and confidence that clearly may affect libido and sexual potency.

Environmental toxin accumulation & oxidative stress

Although this is a huge and very complex field of research, when analyzing the effects of obesity on male's reproductive function, one should not forget the possible influences of environmental toxins. Most of these are soluble in fats and therefore may accumulate in fatty tissues, not only viscerally or subcutaneously, but also around scrotum and testes; for this reason, because of their fat reserves, obese men tend to be at a higher risk [7,8]. An important number of these toxins act as endocrine disruptors, affecting the physiology of HPT axis. Moreover, those substances accumulated around the scrotum might have a direct localized effect on spermatogenesis [76]. In fact, endocrine disruptors have been associated not only with reduced fertility and ED, but also with chronic inflammation, abnormal sexual development, Sertoli-cell-only pattern, altered pituitary and thyroid gland functioning and so on [77]. Only as an example, plasma levels of organ chemicals have been positively correlated with BMI and infertility [63].

With respect to the adipokines secreted by the adipose tissue, a recent study has informed that TNF-α and IL-6 significantly reduce human sperm motility in a time and dose-dependent manner, promoting an increased production of nitric oxide up to pathological levels [78]. Other toxic species that can induce abnormal spermatogenesis are the reactive oxygen species (ROS); these are highly reactive and unstable molecules that may result in oxidative stress inducing significant cellular damage [7]. Numerous authors have noticed that obesity and several of its causative agents, namely insulin resistance and dyslipidemia, are associated with increased oxidative stress [79,80]. The studies of Agarwal *et al.* demonstrated that increasing patterns of ROS are associated with male infertility and may be responsible for semen quality alterations in parameters like sperm concentration, motility and morphology [81]. Briefly, the mechanisms by which oxidative stress alters sperm functional activity involve lipid peroxidation, oxidative DNA damage and protein adducts formation. This result in mitochondrial ROS generation, which damages these organelles and initiate an intrinsic apoptotic cascade as a consequence of which the spermatozoa lose their motility, DNA integrity and vitality [82]. Finally, it has also been informed that

ROS are involved in the pathophysiological mechanisms of ED [75].

Elevated scrotal temperature & sedentary position

It is widely known that the testes descended into the scrotum maintain a temperature 3–4°C below core body temperature, which is compatible with spermatogenesis [83,84]; any elevation in this temperature may have harmful effects on gamete development [82,83]. In fact, it has been informed that heat exposure of the testes provokes hypoxia and oxidative stress on the germinal cells that favors apoptosis [85].

Obesity is often associated with a sedentary lifestyle, which may lead to increased local testicular temperature and result in low sperm count [86]. Moreover, obese men frequently have increased fat deposits in the abdominal area, the upper thighs and surrounding scrotum, all of which may contribute to the mentioned genital heat stress [8,87]. It has been demonstrated that even moderate physiological elevations in scrotal skin temperature are associated with reduced sperm density [88,89].

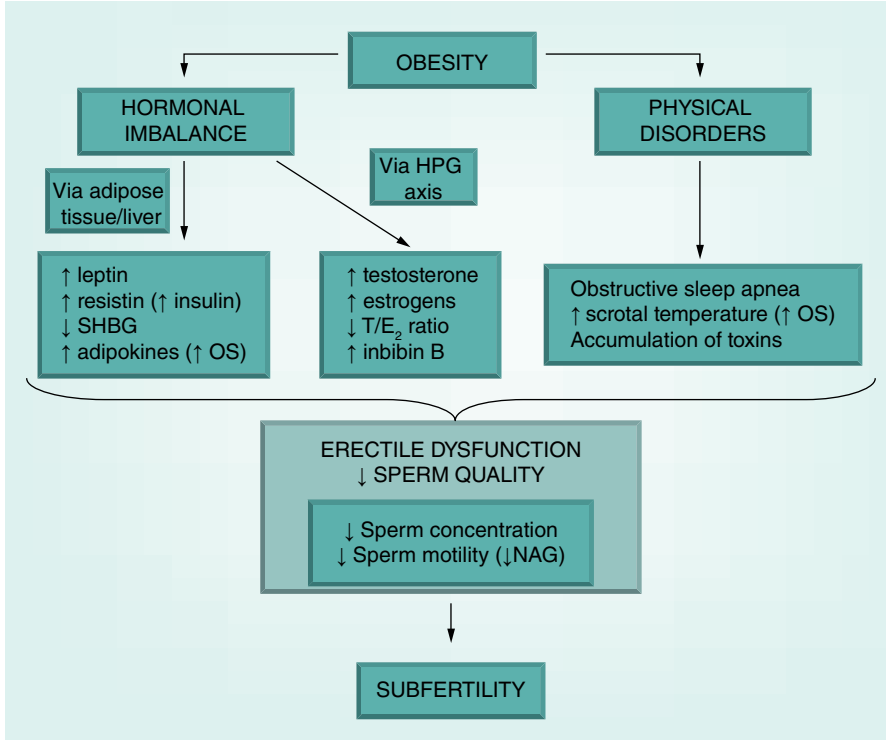

Figure 2. Proposed mechanisms by which obesity may affect men fertility. It is important to remark that not all obese men have impaired sexual function or sperm quality and that no mandatory cause-effect bond can be established.
HPT axis: Hypothalamus–pituitary–testicular axis; NAG: Neutral α-glucosidase; OS: Oxidative stress; SHBG: Sex hormone binding globulin; T/E_2 ratio: Testosterone/estradiol ratio.
Adapted from [96].

Therapeutic tools

In view of the important health problem constituted by obesity, it is promising that some studies have demonstrated that weight loss, naturally or by surgical methods, is able to correct the misbalanced hormonal profile of these men [43,90]. It has been published that those who loss weight by low-energy diets and/or exercise experience an increase in androgens, SHBG and inhibin B levels, in concordance with a decrease in L and insulin [7,8,23,75,91]. Similar results have been obtained after a slim-down procedure by gastrosplasty [46].

Nevertheless, although it would be expected that weight loss also has positive effects on sperm quality, it is not clear if such benefits really exist, especially after massive downsizes, like those provoked by bariatric surgeries. Indeed, positive effects on sperm quality have been reported after diet slim downs [91], but di Frega *et al.* informed about six cases of azoospermia secondary to gastric Roux-in-Y bypass in patients that were previously fertile [92]. Similarly, a recent study by Sermondade *et al.* reported three cases of male patients with normal reproductive hormonal profiles, that after different types of bariatric surgeries suffered severe worsening of semen parameters, including extreme oligoasthenoteratozoospermia; this impairment lasted for at least 15 months postsurgery [93]. So, as Du Plessis *et al.* pointed out, more extensive long-term studies need to be performed to determine the definite effects of bariatric surgery on male fertility; in the meantime, this procedure should not be recommended as a treatment for obesity-linked infertility [7].

Other therapeutic approaches that are relatively successful for managing hormonal imbalance involve GnRH pumps, the injection of human chorionic gonadotrophin [17] or the administration of aromatase inhibitors [7]. This last option has proven to be effective not only in correcting the reproductive hormonal levels but also semen quality [94,95]. Furthermore, it is less expensive than hormonal agonists. Of course, this therapy would only be applicable to those patients with hormonal misbalance linked to hyperestrogenemia.

Finally, scrotal lipectomy is another treatment option to increase fertility in those patients whose excessive fat accumulation may increase scrotal temperature or excess toxin accumulation [4].

In summary, obesity may impact male fertility through different mechanisms that include; malfunctioning of the HPT axis, alterations on spermatogenesis and impairment of sexual health (Figure 2). It is important to keep in mind, nevertheless, that this impairment, when present, seems to be moderate. Nonetheless, since the incidence of obesity is increasing, it is expected that the number of obese men with reduced fertility will rise as well. Physicians must be warned about these risks to appropriately advise couples.

Five-year view

In our opinion, during the next years researchers will enlarge their understanding about the complex net of endocrine and metabolic signals related to obesity that result in an impaired male reproductive function. This intricate mesh of factors will explain why some and not all of obese men are sub/infertile and will demonstrate that obesity is one more of the high number of features that may affect fertility.

Furthermore, we believe that the elucidation of the cellular/molecular mechanisms beneath the harmful effects of obesity on reproduction will identify a small and shared number of final pathways that might explain all the reported detrimental effects.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Since obesity and male subfertility have increased in parallel during the last decades, there might be an association between these two phenomena; this hypothesis has been explored by several researchers.
- The objectives of this review were to summarize what know about the association between obesity and male reproductive function and to analyze the biological significance of this relationship.
- Although there is no consensus, the hormonal profile of obese males seems to be characterized by: a decrease in total testosterone levels and frequently, free testosterone levels as well; decreased gonadotrophin concentrations and an increase in the circulating estrogen levels, provoked by aromatase hyperactivity.
- Furthermore, sex hormone binding globulin and inhibin B are usually reduced in obese males. This last hormone is a marker of the Sertoli cells function and spermatogenesis. It is important to remark that not all the obese men have alterations of the hormonal profile.
- An adipose derived protein that is commonly increased in obese men is leptin. This hormone may exert deleterious effects on the three structures of the hypothalamic-pituitary-testicular axis. Since not only the spermatocytes but also the mature sperm express the leptin receptor, it has been suggested that this substance may directly affect spermatogenesis and seminal sperm quality.
- Although there is no consensus, obesity has been associated with reduced sperm density and decreased sperm motility. We propose that the reduction in sperm motion is a sign of altered epididymal function exerted by obesity. It is important to remark, nevertheless, that in general these seminal alterations are mild, remaining sperm parameters within normal limits. The severity of the damage may be related to the degree of obesity.
- Other factors that may contribute to reduced fertility in obese men are the higher prevalence of obstructive sleep apnea and erectile dysfunction in this population, in addition to the accumulation of environmental toxins that increase the oxidative stress and the presence of elevated scrotal temperature.
- Possible therapeutic tools to treat obesity-linked infertility are weight loss by low-energy diets and/or exercise and managing the hormonal imbalance by gonadotrophins releasing hormone pumps, the injection of human chorionic gonadotrophin or the administration of aromatase inhibitors. Since some negative effects have been found in sperm quality after the drastic weight loss observed after bariatric surgeries, more studies need to be performed to determine the definite effects of this procedure on male fertility.

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Papers of special note have been highlighted as:
• of interest
•• of considerable interest

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