The effect of obesity on sperm disorders and male infertility

Stefan S. Du Plessis, Stephanie Cabler, Debra A. McAlister, Edmund Sabanegh and Ashok Agarwal

Abstract | The results of several studies point to an increased likelihood of abnormal semen parameters among overweight men, and an elevated risk for subfertility among couples in which the male partner is obese. Obesity is, therefore, associated with a higher incidence of male factor infertility. Several mechanisms might account for the effect of obesity on male infertility, both directly and indirectly, by inducing sleep apnea, alterations in hormonal profiles (reduced inhibin B and androgen levels accompanied by elevated estrogen levels) and increased scrotal temperatures, ultimately manifesting as impaired semen parameters (decreased total sperm count, concentration and motility; increased DNA fragmentation index). Neither the reversibility of obesity-associated male infertility with weight loss nor effective therapeutic interventions have been studied in-depth. The increasing prevalence of obesity calls for greater clinical awareness of its effects on fertility, better understanding of underlying mechanisms, and exploration into avenues of treatment.

Du Plessis, S. S. *et al. Nat. Rev. Urol*. **7**, 153–161 (2010); published online 16 February 2010; doi:10.1038/nrurol.2010.6

Introduction

Obesity is a medical condition in which excess body fat, or white adipose tissue, accumulates in the body to the extent that this accumulation of fat might adversely affect health, potentially reducing life expectancy. An individual can be defined as being overweight if their BMI is 25–30 kg/m^2, and obese if their BMI exceeds 30 kg/m^2. However, the distribution of body fat specifically in the central abdominal region has also been used to diagnose a patient as obese and currently waist circumference is believed to be a more accurate marker of obesity. However, these definitions should only be considered as guidelines, as the risk of developing chronic diseases increases progressively when the BMI increases above 21 kg/m^2.[1]

A combination of an increasingly sedentary lifestyle and unfavorable diet in the Western world has resulted in increasing numbers of overweight and obese children and adults. According to the WHO, approximately 1.6 billion adults were classed as being overweight and 400 million adults were obese in 2005.[2] Statisticians have predicted that, by 2015, approximately 2.3 billion adults will be overweight and 700 million will be obese.[2]

Also gaining attention is the reported decline in semen quality and male reproductive potential over the past 50 years. According to Carlsen *et al.*[3] the quality of semen has substantially declined, with the consequent negative effect of poor semen quality on male fertility conceivably contributing to an overall decrease in male reproductive potential. Some studies estimate that male sperm counts continue to decrease by as much as 1.5% per year in the USA; similar findings pertaining to other Western countries have also been reported.[4] Notably, such decreases have not been reported in regions where obesity is less prevalent.[4] Because this decline in fertility has occurred in parallel with increasing rates of obesity, the possibility that obesity is a cause of male infertility and reduced fecundity should be addressed.

Obesity in women is known to contribute to anovulation, a reduced conception rate and an increased risk of miscarriage and prenatal complication.[5] Furthermore, weight loss in anovulatory women restores fertility and increases the likelihood of ovulation and conception.[6] In contrast to the extensive knowledge of the effects of obesity on female fertility, male factor infertility as a result of obesity has been overlooked, even after the discovery of a threefold increase in the incidence of obesity in patients with male factor infertility,[7] demonstrating the need for greater clinician awareness in this area. In this Review, we discuss the influence of obesity on sperm disorders and on male infertility, and present an overview of the potential mechanisms involved as well as possible available treatment options.

Proposed mechanisms

Factors that contribute to the obesity epidemic include a sedentary lifestyle or increased caloric intake, or both; often, these factors occur in conjunction with an unfavorable genotype that predisposes the individual to obesity. Although these factors might help to explain the growing numbers of obese adults and children, there is less evidence explaining how obesity causes male infertility. The mechanisms responsible for effects on male infertility are mostly ambiguous and undefined. Several mechanisms have been proposed, all of which are described below. Most of these mechanisms might contribute to the

Competing interests
The authors declare no competing interests.

Division of Medical Physiology, Faculty of Health Sciences, Stellenbosch University, P.O. Box 19063, Tygerberg 7505, South Africa (**S. S. Du Plessis**, **D. A. McAlister**). Center for Reproductive Medicine, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA (**S. Cabler**, **E. Sabanegh**, **A. Agarwal**).

Correspondence to:
A. Agarwal
agarwaa@ccf.org

Key points

- Male factor infertility is associated with a higher incidence of obesity
- Obesity has been proposed to affect male fertility both directly and indirectly, by inducing alterations in sleep and sexual behavior, hormonal profiles, scrotal temperatures and semen parameters
- Several potential mechanisms might account for the effect of obesity on male infertility
- Obesity might cause aromatase overactivity, affect the endocrinological properties of white adipose tissue, and induce oxidative stress and dysregulation of the hypothalamic–pituitary–gonadal axis
- Weight loss, gastric bypass surgery and the management of hormonal imbalance might prove useful interventions in the reversal of obesity-induced infertility

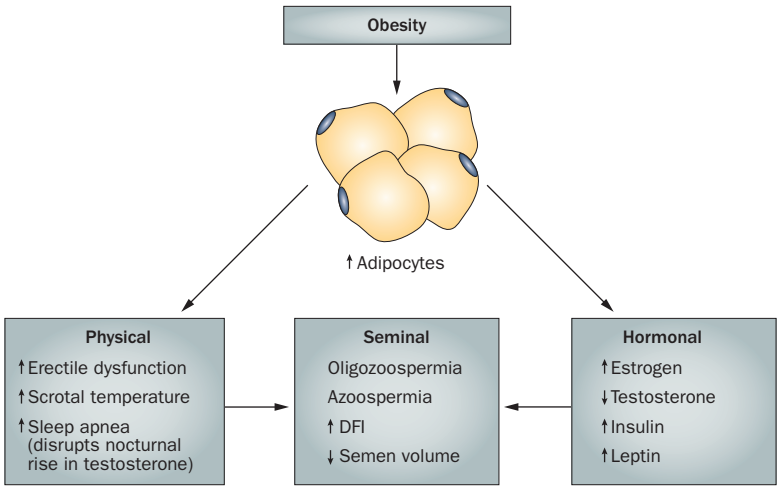

Figure 1 | The role of adipocytes in male infertility. An increase in the size or number of adipocytes as a result of obesity can result in both physical changes and hormonal changes. Physical changes can include an increase in scrotal temperature, an increase in the incidence of sleep apnea, and an increase in erectile dysfunction. Hormonal changes might include increases in the levels of leptin, estrogen and insulin, and a decrease in the level of testosterone. These changes, in turn, contribute to oligozoospermia, azoospermia, an increase in the DFI, and a decrease in semen volume. All three categories of change contribute to obesity-linked male infertility. Abbreviation: DFI, DNA fragmentation index.

dysregulation of the hypothalamic–pituitary–gonadal (HPG) axis, one of the most important functions of which is to regulate aspects of reproduction.

Aromatase overactivity

As obesity is associated with an increase in the number and size of adipocytes, many proposed mechanisms to explain the effect of obesity on male fertility focus on the influence of abnormal levels of adipose-derived hormones and adipokines related to reproductive organs and hormones on fertility. Total body fat, intra-abdominal fat and subcutaneous fat have all been associated with low levels of free and total testosterone in men, and most obese men seeking infertility treatment present with a decreased ratio of testosterone to estrogen.[8,9] This decrease is explained by overactivity of the aromatase cytochrome P450 enzyme, which is expressed at high levels in white adipose tissue and is responsible for a key step in the biosynthesis of estrogens. High levels of estrogens in obese males result from the increased conversion of androgens into estrogens owing to the high bioavailability of these aromatase enzymes.[10] Dysregulated levels of sex hormones can cause great changes in both spermatogenesis and other aspects of male reproduction.

Estrogen is more biologically active than testosterone, even at low concentrations; a small change in the levels of circulating estrogen can, therefore, elicit large downstream effects and can increase the potential for abnormal estrogen activity in the testes. Whereas the complete absence of any estrogen in the testes leads to adverse effects on spermatogenesis and steroidogenesis, abnormally high levels are detrimental to normal male reproductive potential.[11] High estrogen levels have been shown to have a direct deleterious impact on spermatogenesis when tested in animal models.[12] The discovery of estrogen receptors in the male hypothalamus has indicated that estrogen might contribute to low testosterone levels through a negative feedback mechanism.[13] Estrogen acts on the hypothalamus to negatively regulate the release of pulses of gonadotropin-releasing hormone (GnRH) as well as the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland, and estrogen agonists have been shown to have an inhibitory effect on androgen biosynthesis.[13] This observation indicates that estrogens might have a part in regulating the HPG axis, suggesting that any amount of excess estrogen could be detrimental to spermatogenesis.

White adipose tissue as an endocrine organ

White adipose tissue carries out a much more integral role than maintaining physiological homeostasis, regulating metabolism and storing energy. This fatty tissue constitutes up to 20% of male bodyweight and the constituent cells contain a single, large fat droplet. It comprises adipocytes, preadipocytes, macrophages and lymphocytes, making it an important mediator of inflammation and metabolism.[14]

The discovery of the protein hormone leptin confirmed that white adipose tissue also acts as an active endocrine organ, secreting adipose-derived hormones.[15] Leptin is one of a number of proteins secreted from white adipocytes; angiotensinogen, resistin, adipsin, acylation-stimulating protein, adiponectin, retinol-binding protein and tumor necrosis factor, among many others, are also secreted.[16] Excessive fat accumulation characteristic of obesity can, therefore, result in the altered release of adipose-derived hormones and proteins (Figure 1).

Leptin secretion

White adipose tissue is the main site of leptin synthesis and studies show a strong positive correlation between the levels of leptin in serum and body fat percentage. Leptin is a 16 kDa adipokine, encoded by the *ob* gene,[16] that is secreted by adipocytes during the fed state and that stimulates the satiety center. Leptin is produced mainly by adipose tissue, but can also be made by the placenta, stomach and skeletal muscles.[17–19] Besides its action as a

potential satiety factor, leptin fulfills many other functions, such as the regulation of neuroendocrine systems, energy expenditure, hematopoieses, angiogenesis, puberty and reproduction.[20]

As well as a higher prevalence of infertility, obese individuals are reported to have higher circulating levels of leptin than nonobese individuals.[14,15] Although leptin is best known for its role in regulating food intake and energy expenditure via hypothalamus-mediated effects,[21] an increasing body of data suggests that leptin also acts as a metabolic and neuroendocrine hormone, and is involved in glucose metabolism as well as in normal sexual maturation and reproduction.[22] Thus, changes in plasma leptin concentrations can have important and wide-ranging physiological implications. Although leptin deficiency resulting from a mutation in the *ob* gene has been studied extensively and is known to cause obesity, the majority of obese individuals present with elevated serum concentrations of leptin and no mutations in the leptin receptor. These results suggest that obese people are insensitive to the production of endogenous leptin and develop a form of functional leptin resistance.[19]

Leptin levels have also been linked with normal functioning in the reproductive system.[18] Leptin receptors are present in testicular tissue and the discovery of leptin in semen has established a link between this protein hormone and male reproductive function.[17] Jope *et al.*[20] also demonstrated the presence of leptin receptors on the plasma membrane of sperm, suggesting that leptin might directly affect sperm via the endocrine system, independent of changes in the HPG axis.

Excess levels of leptin resulting from increased secretion from adipose tissue are known to have a deleterious effect on sperm production and the production of androgens by Leydig cells.[17] Conversely, a leptin deficiency in mice was demonstrated to be associated with impaired spermatogenesis, increased germ cell apoptosis, and increased expression of proapoptotic genes within the testes.[21] Testosterone replacement treatment has been shown to suppress the levels of circulating leptin. Furthermore increased leptin levels might decrease the levels of testosterone in the serum by inhibitory receptors mediated in the Leydig cells.[17] A study by Hofny *et al.*[22] also found that testosterone replacement therapy decreased leptin levels, although no information regarding the effect of the treatment on semen parameters was reported. By decreasing elevated leptin levels in obese patients, it might be possible to reverse some of the potential suppressive effects of excess leptin on the HPG axis and restore normal spermatogenesis and sperm function.

Resistin secretion and insulin resistance

Resistin is another adipose-tissue-specific factor, which is reported to induce insulin resistance. Almost 80% of men with type 2 diabetes are also obese, and an increase in resistin secretion owing to a higher number of adipocytes links obesity to type 2 diabetes.[16,23] As a consequence of insulin resistance in patients with type 2 diabetes, high circulating levels of insulin are present in the bloodstream. Hyperinsulinemia, which often occurs in obese men, has an inhibitory effect on normal spermatogenesis and can be linked to decreased male fertility. In a group of diabetic men, semen parameters (concentration, motility and morphology) did not differ from the control group, but the amount of nuclear and mitochondrial DNA damage in the sperm was significantly higher.[24] This sperm DNA damage can impair male fertility and reproductive health.

In addition to inducing sperm DNA damage, insulin levels also have been shown to influence the levels of sex-hormone-binding globulin (SHBG), a glycoprotein that binds to sex hormones, specifically testosterone and estradiol, thereby inhibiting their biologic activity as a carrier. High circulating insulin levels inhibit SHBG synthesis in the liver, whereas weight loss has been shown to increase SHBG levels.[25] In obese males the decrease in SHBG means that less estrogen will be bound, resulting in more biologically active, free estrogen. In addition to the conversion of testosterone to estrogen in obese patients, the decreased ability of SHBG to sustain homeostatic levels of free testosterone also contributes to abnormal testosterone levels.[26] This failure to maintain homeostatic levels might magnify the negative feedback effect of elevated total estrogen levels. Even when the presence of SHBG is accounted for, an independent relationship between insulin resistance and testosterone production can still be demonstrated.[8] Therefore, the levels of SHBG might be important only as a marker of altered hormone profiles in obese infertile men.

Environmental toxins and oxidative stress

Most environmental toxins are soluble in fat and therefore accumulate in fatty tissue. Their accumulation not only around the scrotum and testes, but also elsewhere in the body, might disrupt the normal reproductive hormone profile because it has been proved that such toxins are endocrine disruptors in male fertility.[27] As morbidly obese males present with excess scrotal fat, the environmental toxins that accumulate in the white adipose tissue surrounding the scrotum might have a direct localized effect on spermatogenesis in the testes. Lipophilic contaminants are associated with decreased sperm production and thus decreased male reproductive potential, even if fat and fat soluble toxins are not localized in the scrotal area.[28]

Other toxic species that can induce abnormal spermatogenesis are reactive oxygen species (ROS), which are highly reactive and unstable molecules that may result in oxidative stress and that can induce significant cellular damage throughout the body. Numerous authors have noted that obesity and several of its causative agents, namely insulin resistance and dyslipidemia, are associated with increased oxidative stress.[29,30] This association is most likely the result of the higher-than-usual metabolic rates required to maintain normal biological processes and an increased level of stress in the local testicular environment, both of which naturally produce ROS. ROS is an independent marker of male

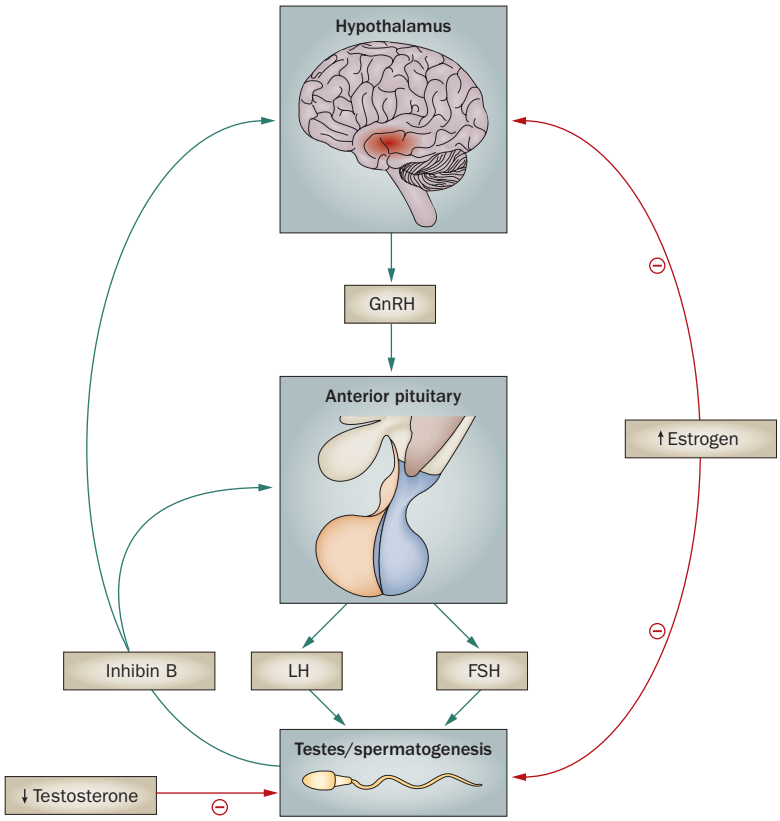

Figure 2 | Dysregulation of the typical hypothalamic–pituitary–gonadal axis as a consequence of obesity. The increase in estrogen and decrease in testosterone levels negatively affects spermatogenesis and regular testicular function. Inhibin B levels are directly related to normal spermatogenesis and thus the low levels of this protein observed in obese males result in abnormal spermatogenesis. The dysregulation of the axis is shown because, despite the low inhibin B levels observed in obese males, there is no compensatory increase in FSH levels as expected. Increased estrogen levels further contribute to the negative feedback effect on the hypothalamus and lead to decreased gonodoliberin and gonadotropin release. Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

factor infertility and can lead to DNA damage, deformity and damaged plasma membrane integrity in sperm.[31] ROS can also affect normal sperm function and motility by damaging sperm mitochondrial genomes, thereby disturbing mitochondrial function and decreasing energy production. In addition, oxidative stress is involved in the pathophysiological mechanism of erectile dysfunction and might explain a higher incidence of this condition in obese patients (see below).[31]

Dysregulation of the HPG axis

Excess body weight can impair the feedback regulation of the HPG axis, and all of the factors above might contribute to, or be a result of, this dysregulation, which can contribute to apparent semen quality abnormalities. Sex steroids and glucocorticoids control the interaction between the hypothalamic–pituitary–adrenal (HPA) and the HPG axes, and any amount of disturbance might, in turn, affect spermatogenesis and male reproductive function. Men of normal weight with low levels of testosterone regularly present with elevated levels of LH and FSH, in contrast with obese men, who usually present with low LH and FSH levels.[32] Inhibin B, a growth-like factor, is produced by Sertoli cells in the testis, and normally acts to inhibit both FSH production and stimulation of testosterone production by Leydig cells in the testis. Surprisingly, the expected compensatory increase in FSH levels in response to low levels of inhibin B is not observed in obese men (Figure 2). A low level of inhibin B might result from the suppressive effects of elevated estrogen levels. A study by Globerman *et al.*[33] also found that there was no increase in FSH levels in obese men whose inhibin B levels remained low after weight loss. Obese, infertile men exhibit endocrine changes that are not observed in men with either obesity or infertility alone. This defective response to hormonal changes might be explained by partial or complete dysregulation of the HPG axis.

Genetic link

Despite there being a known effect of obesity on infertility, many obese males are fertile and have normal reproductive function and fecundity. However, because obesity can result from an unfavorable genotype and because obesity can cause infertility, a genetic link between these two factors might explain this discrepancy. Patients with Klinefelter, Prader–Willi or Laurence–Moon–Bardet–Biedel syndromes all display, to varying degrees, both obesity and infertility. In addition, men who are both infertile and obese show significantly lower testosterone levels than obese fertile men.[7] Although the specific genes involved and mechanism(s) explaining these syndromes are quite well understood, it is possible that other, less severe genetic mutations exist that might explain the discrepancies between obese fertile and infertile men and shed light upon a possible genetic link between obesity and infertility.

Sleep apnea

Sleep apnea is characterized by a fragmented sleep course owing to repeated episodes of upper airway obstructions and hypoxia, and is often diagnosed in obese and diabetic males. Patients with sleep apnea have a disrupted nightly rise in testosterone levels and, therefore, lower mean levels of testosterone and LH compared with controls. In a study into sleep apnea in obese, control and lean patients, Luboshitzky *et al.*[34] concluded that the condition is associated with decreased pituitary–gonadal function and that the accompanying decline in testosterone concentrations is the result of obesity, and to a lesser degree, sleep fragmentation and hypoxia. This disruption has been associated with abnormal spermatogenesis and male reproductive potential.

Erectile dysfunction

Whereas the effects of sleep apnea on reproduction are confounding owing to obesity itself being a cause of infertility, erectile dysfunction is significantly associated with obesity. Patients who are overweight or obese make up of 76% of men who report erectile dysfunction and a decrease in libido.[35] Many studies have found an

Table 1 | Summary of recent studies reporting the relationship between semen quality and obesity

Study	Patients, *n*	Study population	Results/conclusion
Chavarro *et al.* (2009)[42]	483	Male partners of subfertile couples	BMI unrelated to sperm concentration, motility or morphology. Ejaculate volume decreased steadily with increasing BMI levels. Men with BMI >35 kg/m^2 had a lower total sperm count than normal-weight men. Considerably more sperm with high DNA damage in obese men than in normal-weight men
Rybar *et al.* (2009)[65]	153	Male partners of couples attending fertility clinic	No significant differences in the mean BMI and standard semen parameters were found
Hofny *et al.* (2009)[22]	124	Obese fertile and infertile males only	BMI correlated positively with abnormal sperm morphology, correlated negatively with sperm concentration and motility
Pauli *et al.* (2008)[35]	87	Men with BMI of 16.1–47.0 kg/m^2	No correlation of BMI or skin-fold thickness with semen parameters. Obesity is an infertility factor in otherwise normal men
Aggerhlom *et al.* (2008)[28]	2,139	Men in database at University Hospital in Denmark	Marked change in sex hormone profile, but only marginal reduction of semen quality (not significant)
Hammoud *et al.* (2008)[38]	526	Male in couples presenting for infertility treatment	Incidence of oligospermia and prevalence of a low progressively motile sperm count increased with increasing BMI
Agbaje *et al.* (2007)[24]	56	Type 2 diabetic and nondiabetic patients	Reductions in semen volume and a higher mean incidence of nuclear DNA fragmentation seen in diabetic men compared to those without type 2 diabetes
Nguyen *et al.* (2007)[62]	26,303	Retrospective cohort study of pregnancies	Odds ratio for infertility 1:20 for overweight men and 1:36 for obese men relative to men with low–normal BMI; when BMI was divided into eight categories, there was a trend of increased infertility with increased male BMI
Fejes *et al.* (2006)[43]	42	Normal weight, overweight and obese oligozoospermic patients	High BMI group (obese and overweight patients) had lower sperm concentrations than the low BMI group (underweight or normal patients)
Kort *et al.* (2006)[45]	520	Grouped in normal, overweight, obese men	Fewer normal chromatin-intact sperm cells per ejaculate in men with BMI >25 kg/m^2
Zorn *et al.* (2006)[63]	210	Male partners from infertile couples	High leptin levels in obese men not correlated with semen parameters
Fejes *et al.* (2005)[64]	81	Patients presenting with infertility	Waist circumference and hip circumference negatively correlated with sperm count, sperm concentration, total motile sperm cell count and rapid progressively motile sperm count
Jensen *et al.* (2004)[26]	1,558	Young Danish men registering for military service	High and low BMI associated with reduced semen sperm count and concentration
Baccetti *et al.* (2002)[47]	46	Men affected by type 1 diabetes	Severe structural defects in sperm from men with diabetes compared with sperm from controls

association between an increased incidence of erectile dysfunction and an increase in BMI; hormonal dysfunction is central to the connection between obesity and erectile dysfunction.[36] Erectile dysfunction is highly prevalent in men with both type 2 diabetes and obesity, and might act as a forerunner to cardiovascular disease in this high-risk population. Conversely, improved diabetes control and weight loss have been found to improve erectile function.[37]

Elevated scrotal temperature

An elevated BMI can impair or arrest spermatogenesis by causing an increase in scrotal temperature. Increased fat distribution in the upper thighs, suprapubic area and scrotum in conjunction with the sedentary lifestyle often associated with obesity can result in increased testicular temperature.[7,38] Many studies have focused on genital heat stress as a potential cause of impaired semen quality in cases of sedentary occupations, the occurrence of frequent fever and varicocele.[39] Hjollund *et al.*[40] concluded that even a moderate physiological elevation in scrotal skin temperature is associated with substantially reduced sperm concentrations. Additionally Magnusdottir *et al.*[41] found that the duration of sedentary posture correlated positively with increased scrotal temperatures, leading to a decrease in sperm density.

Effects of obesity on male fertility

As discussed previously, various mechanisms can influence and affect male fertility. The effects manifest in both the endocrine and exocrine functioning of the male gonads.

Altered semen parameters

The relationship between male obesity and infertility can be attributed to more than just sexual dysfunction and other altered physical manifestations of obesity. Although spermatogenesis and fertility are not impaired in a majority of obese men, a disproportionate number of men seeking infertility treatment are obese. There have been several studies on the relationship between semen quality and obesity, with an inverse correlation between these parameters frequently being reported (Table 1).

Sperm count and concentration

Obese men are three times more likely than healthy men of normal weight to have a sperm count of fewer than 20 million/ml, also known as oligospermia.[13] Chavarro *et al.*[42] found that men with a BMI greater than 25 kg/m^2 had a lower total sperm count than men of normal weight, and the measured volume of ejaculate decreased steadily with an increasing BMI. Among 1,558 Danish military recruits, there was a negative association between

total sperm count and increasing BMI; there was also a considerable decrease in total sperm count and concentration.[26] These findings have been corroborated by other studies.[22,43] Although several reports exist of a considerable negative relationship between BMI and sperm count and concentration, some discrepancies have been noted; in these studies, a correlation between sperm count or concentration in obese men compared to controls was demonstrated, but was not deemed significant.[28,35,44]

Sperm motility

Some consensus on the effects of obesity on sperm motility has been established, but overall there is no complete agreement. Hofny *et al.*[22] found that the BMI correlated negatively with sperm motility, and Hammoud *et al.*[38] concluded that the incidence of low progressively motile sperm count increased with increasing BMI. Fejes *et al.*[43] concluded that the waist and hip circumference of men correlated negatively with the total motile sperm count as well as the rapid progressively motile sperm count. Despite this evidence, not all studies have included sperm motility within their measurement parameters, and other studies have found no effect of BMI or obesity on sperm motility.[26,35]

DNA fragmentation

Kort *et al.*[45] found that an increase in the DNA fragmentation index (DFI) accompanied an increasing BMI, demonstrating that obesity might compromise the integrity of sperm chromatin. DFI is the percent of sperm in a semen sample that have increased levels of single or double strand breaks in nuclear DNA. A young and healthy man has about 3–5% of sperm with fragmented DNA while a level of 25–30% DFI places a man attempting natural conception at a statistical risk for infertility.[46] An increase in the BMI above 25 kg/m^2 causes an increase in sperm DFI and a decrease in the number of normal chromatin-intact sperm cells per ejaculate, relative to the degree of obesity.[45] Men with type 2 diabetes also present with a significantly higher number of severe structural defects in sperm compared with sperm from controls ($P<0.05$).[47] Typically, males presenting with a high DFI will have reduced fertility and their partners will display an increased incidence of miscarriage as a consequence.[48]

Normal sperm morphology

Measuring differences in the morphology of sperm between obese and normal-weight men can be difficult owing to differences in what is classed as 'normal' morphology and high individual variability within individual patient samples. However, most studies have shown no correlation between obesity and abnormal sperm morphology.[26,35,38,42] In the large retrospective study of Danish military recruits, no association between obesity and poor sperm motility or morphology was reported.[26] Identifying the specific hormones, proteins and mechanisms involved in regulating sperm morphology might help to explain how and why obesity affects normal spermatogenesis.

Abnormal hormone profile

Decreased inhibin B

Inhibin B is the most accurate marker for regular spermatogenesis in all males, and so can be used to predict the quality of sperm and fertility of obese individuals. Inhibin B marks normal Sertoli cell function and associated spermatogenic activity. Measurable decreases in inhibin B levels are indicative of seminiferous tubule dysfunction, therefore subnormal levels clearly reflect irregular spermatogenesis.[35,49] Studies carried out in normal monkeys revealed that inhibin B levels correlate positively with Sertoli cell number (as well as function), and indicate that reduced levels of inhibin B in obese men are likely to signify fewer Sertoli cells than in men of normal weight.[50] The general consensus is that obese men have significantly lower than normal levels of inhibin B, and, indeed, inhibin B serum levels were 25–32% lower in obese men compared with men of normal weight.[28] This marked decrease in the most accurate marker of normal spermatogenesis indicates that the production of male gametes is seriously impaired in obese males.

Decreased testosterone:estrogen

A decrease in the testosterone:estrogen ratio is consistently displayed in obese infertile men. In a study by Aggerholm *et al.*,[28] obese men had 6% higher levels of estradiol and 25–32% lower levels of testosterone than normal men. The severity of obesity determines the degree to which levels of estradiol are increased and testosterone decreased.[13] The increased conversion of androgens into estrogens, which is characteristic of obesity, depresses the function of the pituitary gland by disturbing normal feedback in the testis.

Approaches to treating infertility

It is important that treatment for infertility in obese men differs from that of normal-weight infertile men and that focus is placed on reproductive abnormalities that accompany or are associated with obesity. The unique physiological connections between obesity and the increased conversion of testosterone to estradiol, and the effect obesity has on suppressing GnRH release and spermatogenesis require different management when treating infertility in obese men.

Weight loss

Studies carried out in subfertile females have shown that a reduction in obesity, particularly involving abdominal body fat, is associated with an improvement in reproductive function.[5,6] Weight loss might be an obvious treatment to improve obesity-linked male infertility, but few controlled studies have been done to demonstrate any significant effects. Despite this lack of definitive evidence, there is general agreement among the few studies done. Men who lost weight through natural (diet and/or exercise) methods experienced a high increase in androgen and inhibin B levels and an improvement in semen parameters.[7,17,42] Kaukua *et al.*[51] found that men who participated in a 4-month weight-loss program on a very low-energy diet experienced increases in SHBG and testosterone, and

decreases in the serum concentrations of insulin and leptin. Niskanen *et al.*[52] found similar results in abdominally obese men who, after sustained weight loss, experienced increased testosterone and SHBG levels. In patients who underwent scrotal lipectomy to remove excess fat to relieve elevated testicular temperature, 20% who were previously considered infertile were able to impregnate their partners.[7] This improvement could also be the consequence of the relief from the potential accumulation of local toxins in the testes from surrounding scrotal adipose tissue. Also, a reduction in weight among men with obstructive sleep apnea secondary to obesity increased testosterone levels.[53] Physical inactivity negatively impacts on erectile function, and experimental and clinical exercise interventions have been shown to improve sexual responses. A reduction in caloric intake has been found to improve erectile function in men with aspects of the metabolic syndrome, including obesity and diabetes.[54]

Gastric bypass and banding operations are highly successful in treating morbid obesity. A study by Bastounis *et al.*[55] found that patients who underwent vertical banded gastroplasty experienced a significant decrease in estrogen and an increase in testosterone, SHBG and FSH. Hormonal alterations and diminished sexual quality of life have both been reported to improve after gastric bypass surgery.[56] Even though natural weight loss and even gastric bypass has shown promising results in terms of restoring fertility and surgical treatment has been shown to restore sex hormones to normal levels, some studies indicate that gastric bypass procedure and the drastic weight loss that accompanies it might induce secondary infertility. In a case study by di Frega *et al.*,[57] six healthy, previously fertile males presented with secondary azoospermia following Roux-en-Y gastric bypass surgery. These findings suggest that dramatic weight loss might cause male reproductive dysfunction and even complete arrest of spermatogenesis. Additional data indicate that either the absorption of nutrients required for spermatogenesis was insufficient in these patients following surgery (and presumably could not be restored despite a healthy diet), or that the effect of the surgery on the reproductive system was irreversible. More extensive, long-term studies need to be performed to determine the definite effects of gastric bypass surgery on male fertility; in the meantime, this procedure should not be recommended as a treatment for obesity-linked infertility.

Managing hormonal imbalance

Hormonal agonists

If the patient presents with secondary infertility, successful current treatment options that might be considered involve a GnRH pump or human chorionic gonadotropin (HCG) injection, which acts as an LH analog in the testes, fostering testosterone production.[10] Normal levels of LH stimulate the Leydig cells to secrete testosterone, which might stimulate spermatogenesis.

Aromatase inhibitors

A new line of treatment that has undergone testing for the restoration of fertility in obese men has proven to be effective and less expensive than the use of the hormonal agonists mentioned above. Aromatase inhibitors are designed to interfere with the aromatase P450 enzyme that is highly expressed in white adipose tissue. Currently available aromatase inhibitors include anastrozole and letrozole. Raman and Schlegel[58] tested the effects of anastrazole on nonobstructive azoospermic patients who presented with normal or decreased levels of testosterone and elevated levels of estradiol. Anastrozole treatment normalized the testosterone:estradiol ratio and total testosterone levels, and improved semen parameters.[58] Letrozole was reported to normalize serum testosterone levels in severely obese men with hypogonadotropic hypogonadism,[59] and short-term letrozole treatment normalized serum testosterone levels in all obese men in a study carried out by Loves *et al.*[60] Other studies have presented similar findings using other aromatase inhibitors (for example, anastrozole).[61] The clinical significance of this intervention remains to be established in controlled, long-term studies.

A case study by Roth *et al.*[10] confirmed that this line of treatment might also be effective in the treatment of infertility in morbidly obese men. A morbidly obese man (BMI 54.5 kg/m^2) presenting with azoospermia as a consequence of months of testosterone replacement therapy to treat an expected hormonal imbalance was then treated with anastrozole. After as little as 2 months of therapy, positive treatment effects were seen; after 5 months, semen parameters and serum testosterone levels had normalized; and after 6 months of anastrozole therapy, his wife became pregnant. Although this case is promising evidence for the use of aromatase inhibitors for obesity-linked male infertility, more data on the efficacy and safety of long-term treatment are still needed.

Conclusions

Population-based studies conducted over the past 5–10 years have indicated an increased likelihood of abnormal semen parameters among overweight and obese men and a potential increased chance of subfertility among couples in which the male partner is obese. Reduced androgen and SHBG levels accompanied by significantly elevated estrogen levels are exhibited by obese males. Furthermore, reduced levels of inhibin B correlate with the degree of obesity, but are not accompanied by expected compensatory increases in the levels of FSH or LH. This altered reproductive hormonal profile, which is seen exclusively in obese men, indicates that dysregulation of the HPG axis might explain the increased risk of altered semen parameters and infertility. Additional features associated with male obesity that might contribute to an increased risk of infertility include altered retention and metabolism of environmental toxins, unhealthy lifestyle factors, and sexual dysfunction.

Despite some inconsistency in the results of studies performed to measure the effects of obesity on semen parameters, the consistent decrease in inhibin B levels and increase in leptin levels seen in all obese, infertile patients point toward a true suppression of normal spermatogenesis and sperm quality.

Neither the reversibility of obesity-associated male infertility in response to weight loss nor effective therapeutic interventions have been extensively studied. The increasing prevalence of obesity and apparent simultaneous decrease in male reproductive potential calls for greater clinician awareness of the effects of obesity on fertility, better understanding of underlying mechanisms, and implementation of effective avenues of treatment.

Review criteria

We searched for original articles in MEDLINE and PubMed published between 1995 and 2009. Search terms were "obesity", "male", "infertility", and "sperm". All papers identified were English-language full text papers. We also searched the reference lists of identified articles for other relevant papers.

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