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A hormonal, physical, and proteomic view of obesity-induced effects on male infertility and possible lifestyle modifications

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ABSTRACT

The increasing incidence of obesity worldwide combined with the parallel trend of declining sperm quality has given rise to the notion that obesity and infertility are linked. While investigations of sperm quality in obese individuals have yielded inconclusive results, studies of the adverse hormonal, physical, and proteomic changes induced by obesity are more definitive. Unfavorable hormonal abnormalities reported in obese males that affect reproduction are decreased levels of testosterone, inhibin B, and ghrelin and increased levels of estrogen, leptin, and resistin. Moreover, erectile dysfunction and elevated scrotal temperatures have been associated with obesity and are important physical barriers to successful male reproduction. Recently, important advances have been made in proteomics and factors have been identified in obese individuals that may impair spermatogenesis and sperm quality. Although obesity contributes to a host of adverse effects on the reproductive system, certain lifestyle modifications can be made to alleviate such effects. Natural weight loss and surgical weight loss have demonstrated favorable results in obese patients by restoring normal hormone levels and reversing the effects of both erectile dysfunction and testicular heat stress. Pharmacological interventions have also proven to be promising in combating the effects of obesity. Particularly, aromatase inhibitors such as anastrozole, letrozole, and testolactone, have been reported to decrease the aromatase over-activity and increased estrogen levels present in obese males. An understanding of abnormalities associated with obesity and possible lifestyle modifications may help clinicians effectively guide their infertile obese male patients and increase fertility rates.

1. Introduction

Obesity, defined by the World Health Organization (WHO) as “abnormal or excessive fat accumulation that may impair health,” is a detrimental trend that has been rising worldwide, doubling from 1980 to 2008 [1]. More specifically, the WHO estimates that more than 1.5 billion adults over the age of twenty are overweight and that 1 in 10 adults in the world are obese [1]. It has been suggested that this rising trend of excessive adipose tissue accumulation has not only been caused by an increase in high-sugar and cholesterol-saturated diets, but also by an increase in sedentary

lifestyles[1]. While obesity has been associated with a host of cardiovascular disease, the metabolic syndrome, and a wide variety of endocrine abnormalities, recent research has suggested a potential link between obesity and male infertility[2]. This association has merited investigation over the past decade because of the concurrent trends of rising obesity, increasing male factor infertility, and declining semen quality[3]. Through comprehensive analysis of studies and reviews on obesity and infertility, this chapter aims to elucidate the hormonal abnormalities caused by obesity, its effect-if any-on semen parameters, and possible lifestyle modifications to alleviate the adverse effects of obesity. Ultimately, this chapter will hopefully serve as a consolidation of important and novel information on the rising concerns of obesity and male infertility.

One most common tools of weight measurement used by both the WHO and researchers alike is Body Mass Index (BMI). Specifically, BMI is a ratio of an individual's

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weight in kilograms divided by his height squared in meters. The WHO has set forth standards to classify individuals as underweight, normal, overweight or obese. In particular, a BMI of 18.5–24.99 kg/m² is classified as normal, 25–29.99 kg/m² as overweight, 30–34.99 kg/m² as class I obesity, 35–39.99 kg/m² as severely obese, and a BMI greater than 40 kg/m² as morbidly obese^[1]. While BMI is one of the most common methods for measuring body fat, its effectiveness in assessing visceral fat—the type of fat that is thought to contribute the most to the adverse effects of obesity—has been called into question in recent years. This is likely due to the fact that weight is not directly correlated to fat, since muscle weight differs from fat. As an alternative to utilizing BMI, researchers have started to utilize measures such as waist-to-hip ratio (WHR), waist circumference, abdominal sagittal diameter, computer tomography, magnetic resonance imaging, and ultrasonography^[4]. With regard to WHR, a study published by Noble in *The Western Journal of Medicine* reported that WHR was better correlated than BMI in obese and overweight patients with high cholesterol^[5]. Because adipose tissue tends to accumulate around the midsection, it has been suggested that measuring WHR can properly identify the obese and overweight patients better than BMI. However, BMI remains the most popular method of measurement for assessing obesity, since WHR measurement is a relatively new method. Because of the different measurement systems available to classify obesity, this chapter pays special attention to the manner in which each study recorded their results and made sure that the results are comprehensible based on the standards set by the WHO.

2. Adipose tissue, adipocytokines, and reactive oxygen species

Until very recently, adipose tissue had been merely regarded as a passive storage organ for fat. However, recent studies and discoveries of adipose-specific hormones have illuminated its endocrine function. Adipose tissue secretes two main classes of molecules known as adipocytokines and adipose-derived hormones. These substances are especially significant because they have been implicated in creating a chronic state of inflammation and hyperinsulinemia in obese individuals, both of which have been associated with abnormal reproductive function. While interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) are classified as important adipocytokines, which are cell-to-cell signaling proteins, leptin, adiponectin, and resistin are characterized as adipose-derived hormones which are secreted by adipose tissue^[6]. While leptin and adiponectin play a role in increasing insulin sensitivity, resistin, IL-6 and possibly TNF- α are crucial in the development of insulin resistance. Some studies suggest that the insulin resistance promoted by certain adipocytokines is caused by the oxidation of free fatty acids. The oxidation of the fatty acids creates ATP for gluconeogenesis, thereby increasing glucose levels

and potentially creating hyperinsulinemia and decreased spermatogenesis^[4].

In addition to adipocytokines and adipose-specific hormones compromising male fertility via creating hyperinsulinemia, some play a role in generating Reactive Oxygen Species (ROS). ROS are a group of free radical molecules that contribute to oxidative stress in the body. Oxidative stress, an imbalance between ROS and antioxidant defense mechanisms, has been implicated in adversely affecting semen parameters and male fertility^[7]. With regard to adipocytokines and obesity, both IL-6 and TNF- α promote leucocyte production of ROS. Moreover, leptin has also been linked to increased oxidative stress. While further research is needed to substantiate the effect of BMI on ROS and semen quality, Tunc *et al* found a small but statistically significant correlation between BMI and seminal macrophage activation. However, the effect of such ROS production on semen parameters is unclear, given that the study found no significant decrease in sperm DNA integrity or motility^[8]. Thus, while adipocytokines have important endocrine functions and consequences for the male reproductive system, the effect on eventual reproductive potential remains debatable.

3. Relationship between obesity, sperm parameters, and reproductive potential

Since the trend in rising obesity has been accompanied by a trend of decreasing sperm quality, many scientists have investigated the effect of obesity on sperm parameters. Some of the sperm characteristics that have been evaluated include motility, morphology, viability, concentration, count, and DNA damage. However, studies conducted over the past decade have not yielded consistent results. For example, while Jensen *et al* reported in 2004 a lower sperm concentration, count, and percentage of normal spermatozoa for men with a BMI higher than 25, Fejes *et al* only found significant correlations using a different measure of fat merely a year later^[2,9]. Specifically, Fejes *et al* found that both hip and waist circumference were negatively correlated with total sperm count and motility and that hip circumference was negatively correlated with sperm concentration^[10]. While both of these studies reported an association between increased body weight and semen parameters, the difference in measurement methods for body fat demonstrates the difficulty in achieving standardized results. Evidence of body weight affecting semen parameters is furthered by Sallmen *et al* and Hammoud *et al* who found that BMI has a direct negative correlation to sperm parameters and that BMI is associated with low motile sperm count and low sperm concentration in 2006 and 2008 respectively^[11,12]. Moreover, in 2010, Martini *et al* reported no association between sperm concentration and a negative association between BMI and sperm motility, while Hofny *et al* found that BMI had a positive correlation with abnormal

sperm morphology and a negative correlation with sperm concentration, motility, and testosterone^[13,14]. Additionally, TM Stewart and Tunc et al both found that there was a significantly lower sperm concentration in obese men in 2010^[8,15].

While there are a host of studies that show a negative correlation between increased BMI and sperm parameters, such studies must be treated with caution given the numerous studies that have reported results to the contrary. In particular, Zorn et al found that BMI was not correlated with BMI in 2006 and Aggerholm et al reported no significant differences between sperm count and BMI in 2007^[16,17]. Such evidence was further validated by Pauli *et al* who reported that there was no association between BMI and the semen parameters of density, volume, motility, and morphology in 2008^[18]. More recently, Rybar et al reported that BMI did not significantly affect semen parameters and Chavarro et al found that obese men had no statistically significant differences in sperm concentration, sperm morphology or sperm motility in 2010^[3,19]. In fact, Chavarro *et al* only found lower sperm count and an increased amount of DNA damage among obese men who had a BMI greater than 35. This suggests that the effect of BMI on semen parameters, if any, is restricted to only the most extreme cases of obesity^[19]. Thus, although support exists for the claim that obesity affects reproductive potential, many studies have been published showing no connection between BMI and sperm parameters, thereby making the link between obesity and infertility controversial. The results of studies investigating the relationship between BMI and semen parameters are summarized in Table 1.

4. Hormonal abnormalities in obesity

While the effect of obesity on semen parameters remains widely debated, the hormonal abnormalities present in individuals with increased body mass index are better understood. In normal males, the hypothalamic–pituitary–gonadal (HPG) axis, a neuroendocrine system, ensures that the reproductive system functions properly. Specifically, the hypothalamus secretes gonadotropin–releasing hormone (GnRH) which binds to receptors connected with G proteins on the plasma membrane of pituitary gonadotrophs. Such interaction between GnRH and the receptors facilitates the release of both luteinizing hormone (LH) and follicle–stimulating hormone (FSH). Subsequently, LH binds to receptors on the plasma membrane of Leydig cells, which results in the formation of enzymes involved in testosterone synthesis. Both testosterone and estrogen control LH secretion through negative feedback^[20]. While proper HPG function has been demonstrated in individuals with normal BMI, studies have shown that obesity causes dysregulation of the axis by promoting hormonal abnormalities.

In particular, obesity has been associated with decreased levels of testosterone and increased levels of estrogen in

numerous studies, thereby suggesting that obesity has an adverse effect on the male reproductive system^[19,20]. The suggested mechanism by which this decreased testosterone:estrogen ratio presents in obese individuals is through increased activity of the cytochrome p450 aromatase enzyme, which converts androgens to estrogens^[23]. More specifically, aromatase is an enzyme of the cytochrome p450 family and it is produced from the CYP19 gene. The number of tetranucleotide repeats in intron 4 of the gene has been significantly linked to the increased amount of activity thereof. In 2010, Hammoud et al reported that among severely obese men, increased aromatase activity and estrogen levels were only seen among those who had an increased number of tetranucleotide repeats^[23]. Such a finding suggests that genetics, rather than obesity itself, may be the chief contributor to the abnormal levels of testosterone and estrogen in individuals with increased body weight. Nevertheless, since many studies have not yet examined the genetic influence on aromatase, further research is needed to determine the exact mechanism of aromatase activity in obese individuals.

Another hormonal irregularity that has been reported in obese individuals is an increase in leptin levels^[14,16]. Leptin is a protein hormone that is controlled by the Ob–gene and secreted by adipocytes. Its physiological role in the body is to regulate body weight, but the excess levels that have been reported in obese individuals can have adverse effects, particularly on the male reproductive system^[16,22,24]. Two pathological mechanisms, direct and indirect, have been proposed to account for decreased gonadotropin secretion and spermatogenesis in obese individuals. Normally, Leydig cells stimulate protein kinase A in response to luteinizing hormone and promote steroidogenesis. However, under the direct pathological mechanism, demonstrated most clearly in rats, increased levels of leptin cross the blood–testis barrier. Leptin then acts on Leydig cells to decrease the steroidogenic factor, steroidogenic acute regulatory protein, and steroidogenic mRNAs, thereby inhibiting testosterone secretion. While leptin’s site of action in the direct pathological mechanism is the testis, the indirect mechanism involves the hypothalamus. Normally, leptin crosses the blood–brain barrier through a saturable transport system and binds to leptin receptors on kisspeptin neurons in the brain in order to stimulate gonadotropin release. However, in obese individuals, the increased levels of leptin saturate the blood–brain barrier and do not allow the hypothalamus to be sufficiently activated to release gonadotropins. Thus, at the hypothalamic level, it is actually a deficiency of leptin that inhibits gonadotropin release despite an excess of the hormone being present in the body^[22,25].

Not only are leptin levels disrupted as BMI increases, but ghrelin levels are abnormal as well. Ghrelin is a hormone that is produced mainly in the oxyntic glands of the stomach as well as the intestine and, unlike leptin, it plays an important role in increasing appetite. Moreover,

Table 1

Research Studies of the Effects of BMI on the Reproductive System

Author	Year Published	Findings Related to Sperm Parameters	Findings related to hormones
Chavarro et al	2010	No statistically significant differences in sperm concentration, sperm morphology or sperm motility for obese males. Only those with a BMI greater than 35 had lower sperm count and higher DNA damage.	There were inverse associations of BMI with serum levels of total testosterone, SHBG, and inhibin B, and a positive association with serum estradiol level.
Winters et al	2006	–	Inhibin-B levels declined with increasing obesity in young men (26% lower). SHBG and total testosterone were also lower with increasing BMI, but FSH/LH were unaffected.
Zorn et al	2006	No relationship was found between level of leptin and sperm motility, and morphology. Leptin was correlated negatively with sperm count but this correlation was not present when BMI was used as a control variable.	BMI was negatively correlated with inhibin B, total testosterone, and SHBG.
Martini et al	2010	Negative association found between BMI and motility and rapid motility. No associations between BMI and sperm concentration or testosterone.	Negative association was found between BMI and NAG levels and a positive correlation between BMI and fructose levels.
Pauli et al	2008	No correlation between BMI and skinfold thickness with semen parameters (density, volume, motility, and morphology). Men with paternity had lower BMIs and skinfold thickness.	BMI was negatively correlated with testosterone, FSH, and inhibin and testosterone. BMI was also positively correlated with estrogen.
Hofny et al	2010	BMI had positive correlation with abnormal sperm morphology and negative correlation with sperm concentration and motility.	Obese oligozoospermic had increase in BMI, FSH, LH, estrogen, PRL, and leptin levels. BMI also had a negative correlation with testosterone.
Aggerholm et al	2007	Overweight had lower sperm count and concentration than normal individuals, but obese did not show reduction in sperm count surprisingly. None of these differences were significant.	Testosterone and Inhibin B were lower in obese men compared to normal men, while estrogen was higher.
Fejes et al	2005	There was a negative correlation between hip circumference and sperm concentration. Both hip circumference and waist circumference were negatively correlated with total count and motility. Semen volume was correlated with waist circumference and waist/hip ratio.	BMI and WHR correlated negatively with testosterone, SHBG, and testosterone: estrogen ratio
Hammond et al	2008	BMI associated with low sperm concentration and low motile sperm count.	–
Rybar et al	2010	BMI was not significant in affecting sperm parameters.	–
Sallmen et al	2006	BMI has a direct negative correlation to sperm parameters.	–
<i>O. Tunc et al</i>	2010	Oxidative stress did increase with an increase in BMI due to increase in seminal macrophage activation. But magnitude of increase was small since there was no associated decline in DNA sperm integrity or sperm motility with increasing ROS production. Increased BMI was also found to be linked with a fall in sperm concentration.	Increased BMI was also associated with a fall in testosterone and an increase in estrogen.
Jensen et al	2004	Men with a BMI higher than 25 had a reduction in sperm concentration and total count compared to men with BMI between 20–25. Percentage of normal spermatozoa was reduced in men with high BMI but this was not significant. Volume and percent motility was unaffected.	Serum testosterone, SHBG, Inhibin B was decreased with increasing BMI and estrogen was increased.
TM Stewart	2009	There was a significantly lower sperm concentration in obese men, but this was not accompanied by significant correlations between BMI and any other semen variable.	Correlations with SHBG, inhibin B, and testosterone.
Monti et al	2006	–	Leptin increases and ghrelin decreases were linear over five BMI groups. There was no threshold of BMI where hormone levels change abruptly.

it also influences the male reproductive system through its effects on steroidogenesis and testosterone secretion. In particular, ghrelin binds to ghrelin receptors which are more commonly found in the testis than in other locations

in the body [26]. It has the ability to decrease testosterone secretion by inhibiting enzymes involved in steroidogenesis such as steroid acute regulatory protein (StAR), the P450 cholesterol side-chain cleavage, the 3 β -hydroxysteroid

dehydrogenase and the 17 β -hydroxysteroid dehydrogenase type 3 enzymes. In those who are obese, normal function of ghrelin is disrupted and low levels of the hormone have been reported. While further research is needed to determine the precise mechanism responsible for this decrease, it has been suggested in both animal and human studies that testosterone may control the expression of ghrelin receptors. Since low levels of testosterone are well-demonstrated in obese men, such an explanation for low ghrelin levels is quite plausible[26,27].

Along with testosterone, estrogen, leptin, and ghrelin, another hormonal irregularity that has been shown in obese individuals is a decrease in Inhibin B levels[17-19,21]. Generated by Sertoli cells, Inhibin B plays a vital role in the inhibition of both FSH and testosterone production. Usually, Inhibin B binds to the Activin Type II receptor in order to inhibit activin, which has a stimulatory effect on FSH. Yet, not all activin tissues are deactivated. Rather, it has been suggested that inhibin acts in the pituitary by binding to p120 and betaglycan, two newly discovered inhibin receptors[28]. In individuals with an increased BMI, the decreased levels of inhibin B signals an abnormality in the hypothalamic-pituitary-axis (HPA), since the reduced amount of inhibin B does not result in the expected increase in FSH levels. While the exact pathological mechanism is unclear, decreased inhibin B levels in obese men have nevertheless been associated with abnormal spermatogenesis and infertility[18,29].

Another hormone which potentially indicates obesity-induced abnormalities in the hypothalamic-pituitary-testicular axis is resistin. Resistin is a protein that has been linked with both regulating adipogenesis and promoting insulin resistance. Specifically, gene expression is stimulated during adipocyte differentiation and resistin is secreted by mature adipocyte cells. Because resistin is secreted by adipocytes, it is unsurprising that some studies have found increased levels in obese men. Such an increase in resistin levels has been proposed to adversely affect male reproduction primarily because resistin promotes insulin resistance[4,6]. While the mechanistic pathway of resistin is controversial in humans, Luo et al suggest that resistin exerts its effect on HepG2 cells by signaling the suppressor of cytokine signaling 3 (SOCS-3) pathway, stimulating the expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, and inhibiting the expressions of insulin receptor substrate 2 and glucose transporter 2. Moreover, resistin suppresses the insulin-induced phosphorylation of Akt through an AMPK-independent mechanism[30]. Not only is hyperinsulinemia associated with infertility and reduced spermatogenesis, but it also affects levels of Sex-Hormone-Binding Globulin (SHBG), which normally binds to estrogen and testosterone to suppress their activity. In obese men, studies have reported a decrease in SHBG, which amounts to a surplus of circulating estrogen. This excess of estrogen further

enhances the negative feedback upon gonadotropin release and compromises the efficiency of the male reproductive system[2,9,16,19].

5. Physical ramifications of obesity

Not only does obesity adversely affect hormone levels, but it is associated with detrimental physical effects as well. Two significant physical consequences of obesity include increased incidence of erectile dysfunction and increased scrotal temperature. Specifically, erectile dysfunction—the inability to achieve or maintain an erection during sexual activity—is one of the most prominent unfavorable physical manifestations of increased BMI. Obesity has been linked with a 30% greater risk of erectile dysfunction and 76% of men with erectile dysfunction or reduced libido are overweight or obese[18,31]. It contributes to erectile dysfunction through two main pathways. First, obesity promotes increased activation of the renin-angiotensin system. This system promotes vasoconstriction and disrupts the endothelial lining of the penile vasculature, thereby causing erectile dysfunction. Second, as aforementioned, adipocytokines play an instrumental role in creating chronic inflammation in obese individuals and such inflammation can promote erectile dysfunction. In particular, IL-6 and TNF- α disrupt the penile endothelium by creating high levels of ROS, which decrease Nitric Oxide Synthase (NOS) cofactor tetrahydrobiopterin and delay the hydrolysis of NOS inhibitor asymmetric dimethylarginine (ADMA). Obesity-induced interference with such molecules causes erectile dysfunction because nitric oxide has been associated with facilitating a normal erection[32].

Not only is erectile dysfunction a detrimental physical manifestation of obesity, but increased scrotal temperature is a negative consequence as well. Normally, testicular temperature is three degrees lower than body temperature and helps to promote spermatogenesis; thus, even small increases in scrotal temperature—denoted as testicular heat stress—can impair male reproductive function[22,33]. The adverse effects of heat stress on male reproduction is demonstrated by a study conducted by Mieusset R *et al*, which found that an induction of testicular heat stress significantly decreased spermatogenesis, sperm motility, and sperm count[34]. A more recent study which furthered these results was conducted by Hjollund *et al* in 2000. This study reported that males who had elevated scrotal temperatures showed decreased sperm concentration and sperm count[33]. While many sources of testicular heat stress have been proposed, obesity has been seen as a major contributor to increased scrotal temperature in recent years. Though no studies report scrotal temperatures in obese populations, obese males nevertheless accumulate fat around the suprapubic region due to their inactive lifestyle and excess adipose tissue, thereby potentially producing a high amount of testicular heat stress. Such stress adversely affects reproductive potential by contributing to abnormally low sperm parameters[12,16,34]. The precise pathological

mechanism of heat stress on infertility in humans remains unclear, but studies conducted in mice suggest that testicular heat stress affects spermatogenesis by disrupting junctions in the seminiferous tubules and inducing transforming growth factor- β [35]. Thus, obesity plays an instrumental role in creating physical barriers—erectile dysfunction and testicular heat stress—to successful male reproduction.

6. Proteomics and obesity

While hormonal and physical effects of obesity have been investigated heavily in recent years, the effects of increased BMI on a molecular level remain ambiguous. Nevertheless, recent research is starting to elucidate the association between proteins and obesity. In particular, a study of the sperm proteome by Kriegel et al found that nine sperm proteins were associated with obesity by utilizing the difference gel electrophoresis (DIGE) technique[36]. Evidence of protein involvement in spermatogenesis is furthered by a study conducted by Paasch *et al.* Specifically, this study reported increased levels the eppin protein complex (EPC) proteins in obese individuals. The EPC consists of clusterin, lactotransferrin, and semenogelin-1 which are attached to the proteinase inhibitor eppin. These proteins are located on both the surface of ejaculate spermatozoa and in seminal plasma and have a variety of physiological functions in male reproduction. These functions include protection of sperm, regulation of sperm motility, and preparation of sperm for capacitation. In obese individuals, covalently modified versions of clusterin, lactotransferrin, and semenogelin-1 were present. Specifically, semenogelin-1 and clusterin were much smaller in obese individuals and suggested protein degradation, but lactotransferrin did not show much deviation in molecular weight despite existing in a modified form. While the modified forms of clusterin and semenogelin-1 in obese individuals may contribute to disrupted capacitation and inhibited sperm motility respectively, the function of lactotransferrin in spermatogenesis is unclear[37]. Thus, recent proteomic studies in obese individuals have established that increased BMI adversely affects proteins involved in male reproduction. Nevertheless, further studies are necessary in order to both validate the aforementioned studies and discover additional proteins affected by obesity.

7. Lifestyle modifications to avert the effects of obesity on fertility

While the prevalence of obesity continues to increase worldwide and shows no signs of abating, obesity is nevertheless considered a preventable disease. Of the two main contributing factors to obesity—genetic and environmental—the causal effect of environmental factors is easiest to control and modify. Environmental factors contributing to obesity are entrenched in Western culture and are becoming prevalent in many developing countries as

well. Such factors include the calorie-dense foods available in fast food restaurants and decreased amounts of exercise. These factors have all contributed to a sedentary lifestyle that is quickly becoming a norm for many individuals, and the imbalance between physical activity and caloric intake has contributed dramatically to the rise in obesity[2,38]. Fortunately, the detrimental effects of obesity can be through a variety of lifestyle modifications, including both natural or surgical weight loss and utilization of aromatase inhibitors.

One of the most obvious methods by which obesity's unfavorable effects on the male reproductive system can be averted is through natural or surgical weight loss. Natural weight loss—by means of exercise, decreased caloric intake, and increased nutrition—is considered the optimal method to stem the effects of obesity. In particular, an increase in androgen and inhibin B levels as well as improved semen quality has been reported in obese individuals who used the natural methods of diet and exercise to lose weight[39]. Furthermore, Kaukua *et al* reported increases in SHBG and testosterone and decreases in insulin and leptin in obese individuals who followed a very low calorie diet for four months. Such hormonal changes through natural weight loss methods have proved successful in enhancing fertility by increasing sperm quality[12,40]. Not only does natural weight loss alleviate hormonal regularities induced by obesity, but it also plays a role in reversing erectile dysfunction. Specifically, Esposito *et al* reported that a third of the obese men in their study who had erectile dysfunction regained sexual function following a two-year weight loss regimen of increased physical activity[31]. Thus, while presumably more difficult than other methods of weight loss, natural weight loss can be achieved and can yield favorable results with regard to male reproductive potential.

While natural weight loss has demonstrated is the most favored lifestyle modification to alleviate obesity, surgical methods can be utilized as well when natural weight loss is not feasible. A surgical method which has been demonstrated to be effective is removal of fat from the testicular area and restoring testicular temperature to normal levels is scrotal lipectomy. This is demonstrated by a study conducted by Shafik and Olfat of infertile and fertile male scrotal fat patterns. In particular, they found that scrotal lipectomy improved sperm quality for 65% of patients and helped 20% achieve pregnancies[41]. Not only is scrotal lipectomy a potential lifestyle modification that can reduce the adverse effects of obesity on fertility, but gastric bypass is an effective surgical weight loss technique as well. While studies of gastric bypass in obese individuals have been limited, Bastounis et al found positive results of gastric bypass surgery in 1998 when they studied a group of morbidly obese patients for a year after they had a vertical banded gastroplasty. In particular, they found an increase in FSH, testosterone, and SHBG levels and a decrease in estradiol levels[42]. Although these results indicate that normal HPA function is restored, gastric bypass surgery causes rapid weight loss, which can shock the body and halt spermatogenesis[43]. Nevertheless, many studies have

demonstrated positive effects of surgical techniques in combating obesity–induced male infertility, thereby making it a plausible lifestyle modification.

Although attempting surgical or natural weight loss is a prominent lifestyle modification that can alleviate the obesity and its potential adverse effects on infertility, utilizing aromatase inhibitors is another relatively new method that has been proposed. As aforementioned, the aromatase cytochrome p450 functions in adipose tissue to convert androgen to estrogen^[12]. The overactivity of this enzyme disrupts the HPG axis by creating large amounts of estrogen and altering spermatogenesis by negatively regulating the release of GnRH from the hypothalamus. By contrast, aromatase inhibitors—such as anastrozole, letrozole, and testolactone—counteract the effects of aromatase and the decreased testosterone:estrogen ratio^[21]. For instance, a study by Zumoff et al found that in obese patients who were treated with testolactone, the effects of hypogonadotropic hypogonadism were alleviated and normal HPA function and spermatogenesis were restored. Hence, while aromatase inhibitors have not been widely studied in males, there have nevertheless been indications that such pharmacological interventions may be useful in treating the effects of obesity that are mediated through increased aromatase activity^[44].

8. Conclusion

Thus, the rise of obesity worldwide combined with the trend of decreasing semen quality has caused researchers to posit a potential link between obesity and male infertility. Yet, research has not yielded consistent results regarding the extent to which obesity affects male reproductive potential. While investigation of the mechanisms for obesity–induced hormonal abnormalities is ongoing, numerous studies have nevertheless substantiated that decreased testosterone, ghrelin, inhibin B as well as increased estrogen, resistin, and leptin levels are present in obese males^[6,14,16,18,19,26]. Some of the better understood hormonal mechanisms that may negatively impact spermatogenesis include aromatase overactivity, hypothalamic–based leptin insufficiency and direct leptin saturation in the testis, ghrelin–induced inhibition of StAR and β –hydroxysteroid dehydrogenases, and the stimulation of the SOCS–3 pathway by resistin^[22,23,25,26,30]. Although such abnormalities alter the HPA, these changes do not necessarily alter sperm potential, as demonstrated by studies such as those conducted by Pauli et al, Rybar *et al*, and Martini *et al*^[3,13,18].

While obesity–induced hormonal abnormalities may not affect sperm quality, increased BMI can nevertheless inhibit male reproduction by its adverse physical and proteomic effects. With regard to detrimental physical ramifications, both erectile dysfunction and increased testicular temperature cause infertility and have been associated with obesity. While obesity promotes erectile dysfunction through both stimulation of the rennin–angiotensin system and disruption of proper nitric oxide function, it also may lead to increased scrotal temperature due to accumulation

of adipose tissue around the suprapubic region^[22,32]. Not only does obesity have unfavorable physical effects that contribute to infertility, but its effects on the sperm proteome may impair male reproductive potential as well. While further investigations are needed, increased levels of modified clusterin, lactotransferrin, and semenogelin–1—which are part of the EPC—have been implicated in decreasing sperm quality^[37]. Because obesity–induced hormonal abnormalities, physical alterations, and proteomic changes have been reported to adversely affect male reproductive potential, it is important to elucidate methods by the detrimental effects of obesity can be averted. Fortunately, there are three main lifestyle modifications—natural weight loss, surgical weight loss, and the aromatase inhibitors—that have been implicated in restoring normal hormone levels and improving reproductive potential. In particular, natural weight loss is considered the most favorable to combat obesity and has led to increases in testosterone, SHBG, and inhibin B as well as decreases in leptin and insulin^[39,40]. Moreover, natural weight loss and increased physical exercise can also help reverse erectile dysfunction^[31]. Similarly, studies report that surgical weight loss techniques, such as scrotal lipectomy and gastric bypass, improve semen quality and normalize FSH, testosterone, SHBG, and estradiol levels respectively. While both natural and surgical weight loss have demonstrated positive results in alleviating the effects of obesity, natural weight loss is able to avoid the potential inhibition of spermatogenesis that is caused by rapid weight loss ensuing from some of the surgical techniques^[42]. Not only is weight loss an important lifestyle modification that can be made to mitigate the detrimental effects of obesity, but pharmacological interventions can be made as well. Although studies have been limited, researchers have nevertheless made progress in demonstrating the favorable effects of aromatase inhibitors^[21]. Hence, while there have not been consistent reports about the effects of obesity on infertility, a detailed understanding and continued investigation of the adverse effects to obesity, underlying mechanisms, and lifestyle modifications may have important clinical implications, such as improving semen quality and decreasing the burgeoning rates of male factor infertility^[35].

Conflict of interest statement

We declare that we have no conflict of interest.

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