The role of insulin and leptin in male reproduction

Fanuel Lampiao1, Ashok Agarwal2, Stefan S. du Plessis1

Introduction

A growing body of research has been focusing on obesity and its pathophysiology. Obesity is a cardinal feature of metabolic syndrome, a condition characterized by a group of abnormalities that also includes dyslipidemia, hypertension, and impaired glucose metabolism. In reproductive biology, metabolic syndrome has garnered considerable attention because of the connection that exists between diabetes mellitus (DM), hyperleptinemia, and infertility. Infertility is a common phenomenon in modern societies, affecting an estimated 15% of couples attempting to conceive who are not able to do so within one year. Male factors are believed to play a role in 20 to 50% of infertility cases [1].

Diabetes mellitus is characterized by poor glucose control leading to hyperglycemia. The two types of DM are type I DM, or insulin-dependent diabetes mellitus (IDDM), a condition characterized by an absolute or relative lack of insulin due to autoimmune destruction of the insulin secreting β-cells in the islets of Langerhans in the pancreas; and type II DM, non-insulin dependent diabetes mellitus (NIDDM), characterized by cellular insulin insensitivity despite sufficient insulin levels [2]. Both types of DM are well recognized as a cause of sexual dysfunction, which in turn also contributes to infertility [3]. Diabetes mellitus is thought to affect male reproductive function at multiple levels due to its effects on the endocrine control of the spermatogenesis process and spermatogenesis itself, as well as impairing penile erection and ejaculation [4]. Many studies involving
diabetic animal models have demonstrated an impairment of sperm quality [5, 6], which leads to a reduction in fecundity [6-9]. Furthermore, researchers have reported that men affected with IDDM have sperm with severe structural defects, significantly lower motility [10] and lower ability to penetrate zona free hamster eggs [11]. In recent years, the incidence of NIDDM has increased due to an increase in obesity [3]. An increase in the prevalence of DM will pose a significant problem to human fertility.

Obese individuals also are reported to have higher circulating leptin levels as well as a higher prevalence of infertility [12, 13] than non-obese individuals. Leptin is a 16-kDa protein that is produced mainly by adipose tissue and encoded by the ob gene [14]. It also is produced by the placenta [15], stomach [16], and skeletal muscles [17]. Leptin’s tertiary structure resembles that of cytokines and lactogenic hormones [18]. Leptin is best known as a regulator of food intake and energy expenditure via hypothalamic-mediated effects [19]. An increasing body of data suggests that leptin also acts as a metabolic and neuroendocrine hormone. It is involved in glucose metabolism as well as in normal sexual maturation and reproduction [20]. Thus, changes in plasma leptin concentrations can have important and wide-ranging physiological implications. This review aims to highlight the roles of both insulin and leptin in male reproduction as well as focus on their possible effects at various reproductive levels that contribute to male infertility.

**Endocrine effects of insulin on male reproduction**

The importance of insulin has been demonstrated in male rat reproduction by using streptozotocin to deplete the β-cells of the pancreas, thereby inducing IDDM [7]. Insulin deficiency in these rats led to a decrease in Leydig cell number as well as an impairment in Leydig cell function. This consequently translated to a decrease in androgen biosynthesis and serum testosterone levels. The impaired Leydig cell function and subsequent decrease in testosterone in IDDM could be explained by the absence of the direct stimulatory effects of insulin on Leydig cells, as well as by an insulin-dependent decrease in FSH and LH levels [17].

It also has been reported [10] that insulin plays a central role in regulation of the hypothalamic-pituitary-testicular axis by the reduction in secretion of LH and FSH in diabetic men, as well as in knockout mice lacking the insulin receptor in the hypothalamus. Both the diabetic men and the knockout mice had notably impaired spermatogenesis, increased germ cell depletion, and Sertoli cell vacuolization [10, 21]. Figure 1 show that insulin is required to stimulate the hypothalamus to release gonadotrophin releasing hormone (GnRH).

![Figure 1](image.png)

**Figure 1.** A schematic interaction of insulin, leptin and the endocrine control of spermatogenesis. Diabetes mellitus and obesity have an influence on circulating insulin and leptin levels, respectively. Both insulin and leptin affect the secretion of gonadotrophin releasing hormone (GnRH) from the hypothalamus which subsequently orchestrate the secretion of LH and FSH from the pituitary gland that affect gonadal function and spermatogenesis. Both insulin and leptin can exert direct effects on the testes as well.
hormone (GnRH), which instructs the release of LH and FSH from the pituitary gland. Higher insulin concentrations, such as those found in NIDDM, have been reported to lead to hypogonadism [22] as well as decreased serum testosterone levels [23]. Furthermore, Pitteloud et al. [24] also reported that insulin resistance lead to a decrease in testosterone secretion at the testicular level (Leydig cell) that was not due to changes in hypothalamic or pituitary function. These findings point to a direct action of insulin at the gonadal level (see Figure 1).

Endocrine effects of leptin on male reproduction

Three leptin receptor isoforms have been reported to be present in gonadal tissue, suggesting that leptin could exert a direct endocrine action on the gonads [25-27]. Indeed, studies have shown that treatment of infertile ob/ob knockout mice with leptin restored reproductivity ability [28]. Injecting these ob/ob mice with leptin reportedly caused an elevation in FSH levels and also stimulated gonadal development [29]. Chronic administration of anti-leptin antibody to rats was shown to inhibit LH release [30].

Humans deficient in leptin exhibit effects similar to those observed in animal models. A case study regarding a male with a homozygous leptin mutation reported that he was still pre-pubertal and showed clinical traits typical of hypogonadism and androgen deficiency despite being 22 years of age [31]. Another male subject with a leptin receptor deficiency reportedly showed no pubertal development at either 13 or 19 years of age [32]. Reports like these emphasize the importance of leptin in the onset of puberty in humans.

The mechanisms through which leptin acts are not clearly elucidated as yet but probably involve the hypothalamus and its subsequent effects on the pituitary and gonadal axis. Administration of GnRH to leptin-deficient men has been shown to induce a normal increase in serum LH and FSH levels, while the administration of gonadotrophins increased testosterone levels [31]. As illustrated in Figure 1, this effect may be the result of leptin stimulating GnRH synthesis or secretion from the hypothalamic neurons or secretion of gonadotrophins by the pituitary gland [33].

Effects of insulin on spermatogenesis

Morphological abnormalities have been reported in IDDM human testicular biopsies. These abnormalities included increasing tubule-wall thickness, germ cell depletion and Sertoli cell vacuolization [34]. Morphological and functional spermatozoal abnormalities that have been observed in diabetic animal models appear to be reversible with insulin administration [35, 36].

A significantly lower sperm count and epididymal sperm motility were reported in diabetic rats in comparison to controls [36]. In vitro insulin administration to these retrieved epididymal spermatooza restored their motility to that of normal levels, suggesting a direct effect on spermatooza due to defective carbohydrate metabolism. Studies have reported that insulin as well as insulin-like growth factor I (IGF-I) and IGF-II promote the differentiation of spermatooza into primary spermatocytes by binding to the IGF-I receptor [37]. Evidence also suggests that both the sperm membrane and the acrosome represent cytological targets for insulin [38].

Effects of leptin on spermatogenesis

The importance of leptin during the process of spermatogenesis was demonstrated by the observation that a leptin deficiency in mice was associated with impaired spermatogenesis, increased germ cell apoptosis, and up-regulated expression of pro-apoptotic genes within the testes [39]. This resulted in a reduction in germ cell numbers and the absence of mature spermatooza in the seminiferous tubules. This finding adds further support to the importance of physiological leptin levels in the normal production of male gametes.

Insulin and ejaculated spermatooza

Insulin has been shown to play a central role in the regulation of gonadal function; however, its significance in male fertility is not completely understood and properly elucidated [40]. Until recently, insulin was thought to be produced only by the β-cells in the pancreas of adult mammals [41].

Newer studies, however, have demonstrated that insulin is expressed in and secreted by human ejaculated spermatooza. Both insulin mRNA as well as the actual protein were detected in ejaculated human sperm [41]. Capacitated spermatooza were found to secrete more insulin than noncapacitated spermatooza [41], suggesting a possible role for insulin in sperm capacitation.

Our group, furthermore, has shown the importance of insulin on ejaculated human spermatooza in vitro [42]. Insulin administration to the medium (10 µIU) was found to significantly increase total and progressive motility and enhance hyperactivation characteristics (VCL and ALH) significantly. In vitro insulin administration also led to an increase in spontaneous acrosome reaction, as well as enhanced sensitivity to the progesterone-induced acrosome reaction. Whether this increase was due to the agonists’ effect on capacitation or the acrosome reaction itself is unclear. Our group also demonstrated that insulin increased nitric oxide (NO) production in human
spermatozoa, possibly via the phosphoinositide 3-kinase (PI3K) signaling pathway as evidenced by the reduction in NO production when the PI3K inhibitor wortmannin was administered. Insulin may play a role in enhancing the fertilization capacity of human spermatozoa by increasing motility, NO production and acrosome reaction sensitivity [42].

Leptin and ejaculated spermatozoa

Despite the fact that leptin has been implicated in the regulation of reproduction in humans and animal models and that its specific role in the female reproductive system has been well established, its exact role (s) in the male reproductive system remains to be clarified [43, 44]. Leptin expression in ejaculated human spermatozoa has been demonstrated by identifying its transcripts by means of reverse transcription-polymerase chain reaction; its protein presence was evidenced by Western blot analysis and its localization by immunostaining techniques [45].

The significance of leptin in male reproduction will remain ambiguous for at least a while as results from studies are quite controversial and contradictory. Some studies have indicated positive effects [46], whereas others have reported negative effects of leptin on gonadal function [47]. Seminal plasma leptin levels have been shown to be significantly lower in normozoospermic patients compared with pathological semen samples, and higher leptin levels have shown a negative correlation with sperm function [48]. Conversely, other reports show no correlation between leptin levels and sperm motility or morphology [49]. Capacitated spermatozoa were reported to secrete more leptin than noncapacitated spermatozoa, suggesting that leptin plays a role in the process of capacitation [45]. Moreover, leptin receptors were detected by immunohistochemistry in ejaculated spermatozoa and were localized on the tail area [50]. Similar to what we observed with insulin, our group has demonstrated that in vitro leptin administration increased various motility parameters and NO production and also increased the sensitivity of spontaneous and progesterone-induced acrosome reactions [42].

GLUT8 as a glucose transporter in human spermatozoa

Glucose metabolism is recognized as essential for cell proliferation and survival and usually is carried out through glucose transporters (GLUTs). In mammals there are 14 known members of GLUT proteins [51]. Insulin regulation of glucose transport in target tissues is known to involve the specialized GLUT4 isoforms, which are localized only in insulin-responsive tissues [51].

In conclusion, insulin levels, leptin levels, and male infertility are associated. Decreased insulin levels have been shown to exert adverse effects on reproductive endocrine function and gonadal function, as well as on ejaculated spermatozoa.
function (Table I). On the other hand, decreased leptin levels negatively affect the male’s reproductive capacity by delaying puberty; higher leptin levels have been reported to correlate negatively with human sperm function (Table I).

Insulin and leptin concentrations are a double-edged sword, and a proper balance must be struck for normal reproductive function. Insulin and leptin impairment due to pathologies such as DM, obesity, and metabolic syndrome explain why infertility is connected to these conditions. Despite the fact that the relationship between obesity, metabolic syndrome, DM, and male infertility has been established, the exact mechanisms by which they act have not been elucidated to the fullest. This brief review has

**Figure 2.** Hypothetical model of the functional interaction between insulin and leptin in human ejaculated spermatozoa. Insulin receptor activation and leptin receptor stimulation converge on PI3K via IRS1/2 and JAK/STAT respectively. Activation of the PI3K and PKB/Akt pathway can lead to GLUT8 translocation and insertion in the cell membrane and/or induce NO production

<table>
<thead>
<tr>
<th>Higher concentrations</th>
<th>Absence or lower concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Decreased Leydig cell number;</td>
</tr>
<tr>
<td>(Dhindsa et al., 2004</td>
<td>impaired Leydig cell function</td>
</tr>
<tr>
<td>Low testosterone concentrations</td>
<td>Reduction in LH and FSH; impaired spermatogenesis; increased germ cell depletion; Sertoli cell vacuolization (Brüning et al., 2000; Bacetti et al., 2002)</td>
</tr>
<tr>
<td>Decreased testosterone levels independent of hypothalamus-pituitary-axis (Leydig cells) (Pitteloud et al., 2005)</td>
<td>Sperm morphological abnormalities (Cameron et al., 1985) Reduced sperm motility (Lampiao et al., 2008)</td>
</tr>
<tr>
<td><strong>Leptin</strong></td>
<td>Decreased FSH and LH secretion</td>
</tr>
<tr>
<td>Inverse correlation with percentage motile spermatozoa and straight line velocity (Glander et al., 2002)</td>
<td>Delayed puberty; hypogonadism; androgen deficiency (Strobel et al., 1998) Increased germ cell apoptosis; impaired spermatogenesis (Bhat et al., 2006)</td>
</tr>
</tbody>
</table>

**Table I.** Effects of different insulin and leptin concentrations on male reproductive function
focused only on two hormones i.e., insulin and leptin, that possibly can be implicated under these conditions. Further studies are needed not only to tease out the exact roles each plays, but also to help find possible in vivo and in vitro solutions and treatment regimes for male infertility patients.

References


