Can Obesity Cause Hypogonadism and Infertility in Males? Review of the Literature

Obezite Hipogonadizm ve İnfertiliteye Sebep Olabilir mi? Literatürün Gözden Geçirilmesi

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ABSTRACT Obesity and being overweight have become a major social problem. Globally around 1.6 billion people are overweight and 300 millions of them are clinically obese. It doesn't only affect only the developed countries but incidence appears to be increasing in the developing countries. Besides the well known risks such as coronary heart disease, serebrovascular disease and obesity related hypoventilation syndrome, it is also related with reproductive problems in males. Adipose tissue is an endocrine, paracrine and an autocrine organ and plays a role in pathophysiology of many disorders including hypogonadisim. Obesity reduces male fertility and harms endocrinologic and sexual mechanisms. In obese patients we can detect isolated hypogonadotropic hypogonadism which can be proven biochemically and is directly correlated with the severity of obesity. There are many studies about effects of obesity on well known traditional sperm parameters such as sperm count and morphology. The recent animal studies show that simple diet and exercise interventions can be used to reverse the damaging effects of obesity on sperm function. In this article we have aimed to discuss the effects of obesity on male reproductive system such as sperm parameters and endocrinologic influences.

Key Words: Obesity; hypogonadism; infertility

ÖZET Obezite ve fazla kilolu olmak global olarak majör sosyal bir problem haline gelmiştir. Tüm dünyada 1,6 milyar kişi fazla kilolu olup, bunların 300 milyonu klinik açıdan obezdir. Bu sorun sadece gelişmiş ülkeleri değil gelişmekte olan ülkeleri de etkilemektedir. Obezite ile ilişkisi gösterilmiş klasik risk faktörlerinin yanı sıra (koroner arter hastalığı, serebrovasküler olay, obezite ilişkili hipoventilasyon sendromu gibi) bu metabolik bozukluğun, erkek hipogonadizmi ve infertilitesi ile ilişkili olduğu da düşünülmektedir. Adipoz doku otokrin, parakrin ve endokrin yollar vasıtası ile hipogonadizm dahil birçok hastalığın patogenezinde rol oynar. Obez hastalarda biyokimyasal olarak kanıtlanabilen ve doğrudan obezitenin ciddiyeti ile ilişkili hipogonadotropik hipogonadizm mevcuttur. Obezitenin sperm sayısı ve morfolojisi gibi geleneksel sperm parametreleri üzerindeki negatif etkisini gösteren birçok çalışma bulunmaktadır. Son dönemde yapılan hayvan çalışmalarında diyet ve egzersiz ile obezitenin sperm fonksiyonlarına olan negatif etkilerinin geriye çevrilebileceği gösterilmiştir. Bu makalede amacımız obezitenin, sperm parametreleri ve hormonal sistem üzerindeki etkilerini gözden geçirmektir.

Anahtar Kelimeler: Obezite; hipogonadizm; infertilite

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Obesity and being overweight have become a major social problem. Globally around 1.6 billion people are overweight and 300 millions of them are clinically obese.[1] Incidence of obesity has increased up to three times since 1980 in North America, United Kingdom, Middle East, Australia and China.[1] It doesn't only affect the developed countries but in-

cidence is also increasing in the developing countries. According to WHO (World Health Organisation), the term overweight is defined as BMI (Body Mass Index) (weight/height^2) being over 25 and obesity as BMI over 30. Other measurements which can be used in researches to define obesity are waist and hip circumferences and their ratios to each other.[2] Obesity is closely related with increased risk of coronary heart disease, cerebrovascular disease, hypertension and obesity related hypoventilation syndrome. The major cause of obesity is thought to be highly palatable and energy rich food containing sugar and saturated fat, consumed in the daily diet. Negative effects of obesity on male fertility have been known since 10th century. Persian physician Avicenna has mentioned about this disorder in his book "Rules of Medicine".[3]

In obese patients we can detect isolated hypogonadotropic hypogonadism which can be proven biochemically. Its incidence is directly related with severity of obesity. In a study, 36% of 160 obese males, referred to a certain center for either medical or surgical therapy, were detected to have idiopathic hypogonadotropic hypogonadisim. Prevalence was 7.4% in the patients whose BMI was 30-35 whereas it increased linearly to 59% among the ones whose BMI was above 50.[4] Obesity related hypogonadism and infertility may be due to Luteinising Hormone (LH) supressive effect of estrogen excess, suppressive effect of leptin on LH or hypoventilation related hypothalamo pituitary dysfunction.[5-7] In this review we have aimed to overview the literature about the related topic.

SPERM PARAMETERS IN OBESE PATIENTS

There are many studies about effects of obesity on well known traditional sperm parameters (concentration, motility, morphology) in the literature (Table 1). In some of the studies, a negative correlation has been found between sperm count and BMI, whereas in the others that kind of relation could not be shown.[8-10] In a recent metaanalysis, 13 077 males were evaluated and sperm count abnormality was detected to be more prevelant among overweight or obese individuals compared to ones with normal body weight.[11] In another study conducted with 1558 males, sperm concentration and total sperm count were lower in a subgroup of patients whose BMI was above 25 compared to ones with ideal weight but semen volume, sperm morphology or motility were similar between the groups.[12]

TABLE 1: Summary of the studies in overweight and obese patients that investigated the correlation between body weight and semen parameters.

Semen parameters	Study	Result
Semen concentration	Jensen et al. (2004)	Normal
	Chavarro et al. (2010)	Normal
	Ramlau Hansen et al. (2010)	Normal
	Quin et al. (2007)	Decreased
Sperm motility	Jensen et al. (2004)	Normal
	Magnusdottir et al. (2005)	Normal
	Aggerholm et al. (2008)	Normal
	Chavvaro et al. (2010)	Normal
	Kort et al. (2006)	Decreased
	Hammoud et al. (2008)	Decreased
Sperm morphology	Quin et al. (2007)	Abnormal
	Chavarro et al. (2010)	Abnormal
	Jensen et al. (2004)	Normal
	Hammoud et al. (2008)	Normal
	Ramlau Hansen et al. (2010)	Normal
Sperm DNA integrity	Kort et al. (2006)	Decreased

In one study, 274 males with normal sperm counts were examined and sperm concentration was found to be relatively lower in the subgroup of patients who were overweight or obese compared to ones with normal weight.[13] Obesity can also affect sperm motility. In one study there has been shown a negative correlation between number of motile sperms and BMI (mean number for sperms with normal motility was $18.6x10^6$ in normal individuals and it was $0.7x10^6$ in obese ones). In the same study, the chromatin content of the sperms with normal motility in each ejeculation was found to be decreased in obese patients.[14] In all studies that we have mentioned here, there might be factors such as lifestyle of the patients such as cigarette, alcohol or drug consumption or accompanying comorbid conditions which might affect study results and make it difficult to inter-

prete the outcomes. For that reason, animal models are formed which can reflect and demonstrate male obesity and reveal semen parameters. In that kind of studies, when obese animals were fed with high fat diet, it was observed that sperm numbers were lower and number of sperms with normal morphology or motility was also decreased.[15-18]

Recently, it has been thought that genetic content and molecular morphology of the sperms are also as important as traditional sperm parameters for establishing a healthy embryo. Integrity of the sperm DNA is closely related with succesful fertilization and normal development of embryo.[19]

In a study, sperm chromatin integrity was evaluated by using flow cytometry and it has been observed that as the BMI increased, DNA fragmentation index also increased and they were found to be positively correlated with each other (fragmentation index was 19.9% in normal weights, 25.8% in overweights and 27% in obese patients).[20] Chavarro et al. has proposed that BMI was positively correlated with DNA damage in sperms but they could not show any correlation between sperm count, morphology and BMI.[21]

Effects of obesity on the sperm parameters are suggested to be multifactorial. The first mechanism is disturbed hypothaloma-pituitary axis. Increased aromatization of androgens to estrogen and hyperestrogenemic state reduces the gonadotropins which is accompanied by low testosterone levels which in turn causes disorders in spermatogenesis.[22] Moreover, some authors suggest that hyperinsulinism in obese patients can reduce sex hormon binding globulin levels which can further increase the negative inhibitory effect of estrogen on gonadotropins.[23] Furthermore, increased endorphin levels in obesity may play a negative role in regulation of GnRH (Gonadotrophin Releasing Hormone) and LH pulses.[24] Some researchers suggest that obesity has a direct inhibitory role on spermatogenesis and FSH and inhibin levels decrease in severe cases.[25] Another hypothesis suggest that increased abdominal, hip and even scrotal adipose tissue would cause increased temperature in scrotum and disrupts spermatogenesis.[26] That hypothesis is supported by a study in which semen quality had increased after surgical removal of excess fat layer in scrotum.[27] However it is difficult to draw any conclusion from the previous study since a control group composed of obese patients without any infertility problem did not exist. Other factors that can affect spermatogenesis in obese patients are metabolic parameters such as lipid profiles. Increased cholesterol and tryglyceride levels can decrease semen quality and lead to infertility.[28] In one study incidence of dyslipidemia in male partners of infertile couples was reported to be 65%.[29]

Increased lipid peroxidation in obesity is suggested to be toxic on spermatozoa. This hypothesis was supported by an in vitro study which showed that increased endogenous oxygen radicals caused DNA fragmentation in sperms.[30] Oxidative stress may cause lipid peroxidation on sperm membrane which may be related to decreased sperm motility.[31] It has also been shown that antioxidants can protect sperm DNA from oxidative stress in animal models.[32]

MALE OBESITY AND HORMON PROFILE

Obesity reduces male fertility and make it by endocrinologic and sexual mechanisms. In obese males there is hyperestrogenic hypogonadotrophic hypoandrogenism. Total, free testosterone and gonadotrophin levels are all low. In these inviduals increased aromatization is responsible for the increased estron and estrodiol levels. White adipose tissue is the site for aromatization. Estrogen itself directly affects spermatogenesis negatively which was observed in individuvals with the history of diethylstilbesterol exposure.[33] Estrogen has effects on hypothalamus and change GnRH pulsatility and supress gonadotrophins. Formed hypogonadotropic environment would reduce testicular functions and testosterone levels both in the circulation and testis.[34] When aromatase inhibitors were given to obese males, serum LH and testosterone levels were observed to increase.[35] Anti estrogen clomiphene citrat similarly increased gonadotropin and testosterone levels in those patients.

Inhibin B is an indicator of sertoli cell function. Inhibin levels are also found to be lower in obese patients than the normal ones. Winter et al. has confirmed this hypothesis in a study and found that inhibin levels were lower in young adult obese patients compared to sex and age matched individuals with normal weight.[36] Normally low inhibin should increase FSH secretion however in obese patients it can not increase because of the supressive effect of high estrogen level in the circulation.[37] Because of insulin resistance and hyperinsulinemia in obese patients, sex hormon binding globulin and albumin levels decrease which will lead to increased free testosterone and indirectly magnify negative feed back effect of estradiol on gonadotropins.[38] When massively obese patients lose weight and return to their ideal weights sex-hormone-binding globulin and its steroid binding capacity also returns to normal.[39,40]

Some other factors such as hypoventilation and endorphins can worsen hypoandrogenemia.[41,42] One possible explanation about obstructive sleep apne syndrome related decrease in testosterone may be that the sleep-related rise in serum testosterone levels is linked with the appearance of first Rapid Eye Movement (REM) sleep and fragmented sleep disrupts the testosterone rhythm with a considerable attenuation of the nocturnal rise only in subjects who did not show REM sleep.

Increased endogenous opioid inhibition of the hypothalamic GnRH pulse generator resulting in insufficient stimulation of the pituitary gonadotrophins has been proposed as another possible mechanism. This hypothesis was confirmed in one study showing that obese males were more sensitive to the LH-elevating effects of the opiate antagonist, naloxone, than men of normal weight and gonadal status.[43]

Adipose tissue is an endocrine, paracrine and an autocrine organ and plays a role in pathophysiology of many disorders. Substances produced by adipose tissue such as leptin, adiponectin, visfatin, apelin, vaspin, hepcidin, omentin, TNFα (Tumour necrosis factor alpha), monocyte chemoatractant protein and plasminogen activator inhibitor are active hormones.[44] Leptin is a molecule which was discovered in 1994 and it is known to supress hunger decreases feeding and increase fat metabolism. Moreover leptin also supresses ovarian follicular development in females, decrease stereidogenesis and cause reproductive abnormalities in obese patients.[45] Leptin deficiency or receptor mutations have been detected to be related with early onset obesity, delayed puberty and hypogonadisim.[46] Testosterone and leptin levels are negatively correlated. In one study, Leptin receptor expression on Leydig cells was inversely correlated with serum T concentration. The dysfunction of spermatogenesis was found to be associated with an increase in leptin and leptin receptor expression in the testis.[47] In another in vitro study it was detected that leptin concentration in obese individuals were capable of supressing testosterone production via inhibiting conversion of 17 OH progesterone to androgens.[48] Spermatocytes possess leptin receptors on them and an increase in intratesticular leptin can disrupt spermatogenesis.[49] Resistin is an another protein that owes its name to its suggested role as an insulin resistance mediator. Resistin regulates glucose homeostasis and insulin sensitivity.[4] It is implicated in glucose metabolism. Resistin is secreted by cultured adipocytes and can also be detected in plasma, whereas in humans, resistin seems to be produced by circulating monophages and monocytes.[50] In an in vitro study, the reduction in pituitary concentrations of resistin in obese mice compared with control mice and the co-localisation of resistin protein in rodent hypothalamus with neurons involved in feeding behaviour have led the authors to suggest a relation between resistin and the central control of feeding and obesity.[51] On a peripheral level, the hormone itself was detected by immunochemistry in both Leydig and Sertoli cells. Expression of resistin in testes is driven by gonadotropins. Resistin increases basal and human chorionic gonadotropin (hCG)-stimulated T concentrations, in a dose-dependent way. All the above may show that resistin has a hormonal effect on the testes linking energy homeostasis with reproduction.[52]

GENETICS

Obesity related hypogonadisim should have a genetic component because only some portion of obese individulas suffer from hypogonadisim.[53] Overweight and obesity are complex traits, in which interactions between environmental and multiple genetic factors lead to varied clinical presentations. Genetic component is well known in some syndromes characterised by obesity and hypogonadism such as Prader WMoon-Bardet-Biedl syndrome. The most strong association with obese susceptibility has recently been revealed for gene variants of fat-mass-and obesity-associated (FTO).

CONCLUSION

There is emerging evidence that male obesity negatively impacts fertility through changes in hormone levels, as well as direct changes to sperm function and sperm molecular composition. Obesity related hypogonadisim should be a concern for urologists, endocrinologists and even for surgeons who can perform bariatric surgery. Additionally, the recent animal studies showing that simple diet and exercise interventions can be used to reverse the damaging effects of obesity on sperm function. So, the fact that "obesity leads infertility" can be used as a public message in order to give another reason for obese people to lose weight.

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