Review Article
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Obesity and male reproductive functions

Abstract

Obesity is associated with multiple metabolic disorders and the impact of obesity on reproductive function in males has been recognized gradually. Obesity is associated with complex hormonal changes both at the level of the hypothalamus and pituitary as well as testis. The altered hypothalamic pituitary testicular (HPT) axis along with hypothalamic pituitary adrenal (HPA) axis and chronic inflammatory changes impacts the testicular function.

Methods: PubMed, Cochrane, Google Scholar, Embase database search for publications in English language until March 2108 pertaining to obesity and male reproductive function was performed

Result: The leptin resistance in obesity contributes to a decreased GnRH release, which in turn leads to a decrease in LH and FSH affecting steroidogenesis and spermatogenesis. The Hypogonadotropic hypogonadism can also be attributed to reduced kisspeptin expression in overweight and obese. There is also a reduction in serum total and free testosterone and SHBG levels. Obesity is also a chronic stress with a bidirectional relationship with cortisol levels. Obesity negatively impacts the semen parameters affecting male fertility.

Conclusion: There is a complex relationship between the adipose tissue, leptin and the inflammatory system with the HPT and HPA axis function. Understanding the mechanisms in detail could lead to potential therapies for the common obesity-related reproductive dysfunction.

Keywords: obesity, hypothalamic pituitary testicular axis, semen parameters

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Abbreviations: ARC, arcuate nucleus; ARKO, androgen receptor knock out; AgRP, agouti related protein; AMH, anti mullerian hormone; AVP, arginine-vasopressin; BMI, body mass index; CART, cocaine and amphetamine regulated transcript; CRH, corticotropin releasing hormone; CRF, corticotropin releasing factor; FSH, follicle stimulating hormone; GABA, gamma amino butyric acid; Glut 4, glucose transport receptor 4 GPR54, G protein coupled receptor 54; GnRH, gonadotrophin releasing hormone; HFD, high fat diet HPA hypothalamic pituitary adrenal axis; 11β HSD, 11 β hydroxysteroid dehydrogenase; IL, interleukins LH, luteinizing hormone; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; MSH, melanocyte stimulating hormone; NIRKO, neuron specific insulin receptor knock out; NPY, neuropeptide Y; POMC, propriomelanocortin; PSA, prostate specific antigen; SHBG, sex hormone binding globulin.

Introduction

More than one third (36%) of U.S adults have obesity.[1] It has become a major challenge to health across the globe. Obesity causes a staggering burden on the health care system. Obesity has a great impact on the cardiovascular, endocrine and renal system. Off late the effect of obesity on the reproductive system has been highlighted. Much has been talked about obesity and female infertility. The literature among obese men is slowly catching up. This review highlights how obesity affects male reproductive system and function. BMI has been a tool to predict obesity related morbidities. However a Canadian study pointed out that waist circumference is a better predictor of cardiovascular and cancer mortality in comparison to BMI.[2] This can be due to the reason that excess weight stored as visceral adipose tissue is more closely linked to cardiovascular outcomes than subcutaneous adipose tissue. Other markers of obesity are visceral adipose tissue and intrahepatic triglyceride content.[3] However we do not have a specific marker to predict obesity-related reproductive outcomes.

Aims and objectives

The aim of this study is to give a broad overview of the effect of obesity on pathophysiological changes in reproductive system in men.

Methodology

We searched the following database PubMed, Embase, Cochrane review and Google Scholar. Only English articles were included in the study. The articles from the last 20 years were included. Keywords used for search included Obesity and reproductive functions, Obesity and Hypothalamic Pituitary testicular axis, Obesity and Hypothalamic pituitary adrenal axis, Obesity and semen analysis, Obesity and Kisspeptin, Obesity and testis, Obesity and Insulin, Obesity and Inhibin, Obesity and leptin. Obesity and Prostate, Obesity and cortisol Obesity and testicular functions and Obesity and growth hormone, Obesity and Melanocortin system, Obesity and erectile dysfunction, Obesity and chronic inflammation, Obesity and Liver metabolism, Obesity and testicular temperature regulation. A further search was done using citation tracking. This review excluded obesity in association with other endocrinological disorders and obesity with infertility.

Affect on hypothalamic-pituitary-testicular axis

The Hypothalamic- Pituitary - Testicular axis regulates testicular

function. Gonadotropin-releasing hormone (GnRH) released by hypothalamic neurons stimulates the release of pituitary gonadotropins FSH and LH, which act on the testicle to stimulate spermatogenesis and steroidogenesis, respectively. The hypothalamic gonadotropin is under intense positive and negative feedback regulation in the body. Also, the energy levels in the body have a crucial impact on the secretion of gonadotropin. Obesity is a state of excess energy and thus excess adipocytes. Leptin is one of the Adipokines secreted by adipocytes. Leptin receptors are present in the Hypothalamus and regulate GnRH secretion.[4] However, the action of Leptin on GnRH neurons is indirect.[5] The action of leptin on GnRH neurons is mediated by neuropeptides such as neuropeptide Y, agouti-regulated peptide (AgRP), proopiomelanocortin (POMC) and Gaba-aminobutyric acid (GABA).[6] The GABAergic neuron act as a bridge for reflecting the metabolic changes on the reproductive axis. Leptin has shown to increase the firing of GABAergic neurons and thus increase GnRH levels.[6,7] Studies have shown that leptin stimulates GnRH pulsatility and not amplitude.[8] Obesity is a state of leptin resistance that might contribute to a decreased GnRH release. Thus in obesity, the leptin resistance might contribute to a decreased GnRH release, which in turn leads to a decrease in LH and FSH affecting steroidogenesis and spermatogenesis. Kisspeptin is neuropeptide derived from Kiss 1 gene.[9] Kisspeptin also regulates the pituitary hormones. Kisspeptin infusion has been shown to increase LH mainly and FSH, and testosterone to a lesser extent.[10] Kisspeptin action is different in men and women. Kisspeptin neuron exhibits sexual differences in both number and expression of neurons.[11] Studies in lower animals have shown that obese males have suppressed hypothalamic Kiss-1 expression despite low testosterone and decreased LH response to kisspeptin.[12] Kisspeptin infusion in obese overweight type 2 diabetes mellitus men lead to increased LH pulse frequency and secretion and can be used as a novel therapeutic agent.[13]

Obesity and growth hormone

Growth hormone plays an important role in metabolism particularly lipolysis. Growth hormone secretion is regulated by the hypothalamus through Growth hormone-releasing hormone which stimulates the release and Somatostatin which inhibits the secretion. Growth Hormone secretion induced by growth hormone releasing factor and insulin induced hypoglycemia is decreased in obesity.[14] This decrease in growth hormone decreases lipolysis and increases fat stores further. These changes seen in obesity have been reversed with weight loss.[14,15] Exercise can improve the growth hormone release and thus it can be an important non-pharmacological method to decrease obesity.[16]

Obesity and hypothalamic pituitary adrenal axis

Role of glucocorticoids in human obesity can be due to alteration in Hypothalamic pituitary adrenal (HPA) axis. Chronic stress leads to weight gain, especially in men. Obesity is a state of chronic stress which increases cortisol secretion and favors central obesity further. The relationship between obesity and cortisol appears to be bidirectional. The negative feedback mechanism by which cortisol suppresses its own levels plays a crucial role in the hypothalamic pituitary adrenal axis. Few studies have shown blunted negative feedback response in obese men.[17] Another study has shown that the HPA axis is sensitive to negative feedback by dexamethasone in both obese men and women.[18] However, this study showed that abdominal obesity in women did affect the suppression of the HPA axis.[18] Obese individuals have shown higher ACTH response to CRH and AVP(Arginine-Vasopressin) stimulation.[19] The Hypothalamic Pituitary-adrenal axis interaction with androgen and Androgen Receptor (AR) helps to maintain normal feedback of glucocorticoid system. Studies in Androgen Receptor Knock-Out mice model showed hypertrophic adrenal glands and excess glucocorticoid production and obesity proving that Androgen/AR controls the glucorticoid system through negative feedback.[20] The HPA axis also regulates energy homeostasis in the body by regulating calorie intake during chronic stress and further contributing to obesity. Glucocorticoids levels are also controlled locally by the action of 11-β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) which converts inactive cortisone to cortisol in different tissues such as adipose tissue and liver and 11- β Hydroxysteroid dehydrogenase type 2 which converts cortisol to cortisone.[21] Levels of 11 βHSD 1 has been shown to be high in Liver correlating with Subcutaneous and visceral adipose tissue in morbidly obese patients indicating its role in pathophysiology of obesity.[22]

Melanocortin system and male obesity

The nodal center for metabolic control resides in the Hypothalamus at the level of the arcuate nucleus (ARC) and ventromedial nucleus of Hypothalamus. In the ARC, two neuropeptides play significant roles in the control of metabolic function through the melanocortin system: α-melanocyte-stimulating hormone [MSH; agonist of the melanocortin-3 and melanocortin-4 receptors (MC3R and MC4R)] and the agouti-related protein (AgRP; inverse agonist of MC3R and MC4R),[21,22] produced by proopiomelanocortin and cocaine and amphetamine-regulated transcript (POMC/CART) and neuropeptide Y (NPY)/AgRP neurons, respectively. The POMC and CART neurons have a potential Anorexigenic effect whereas AgRP and NPY have orexigenic effect.[23] So in a state of negative energy balance AgRP neuron expression is increased and vice versa. Both AgRP and POMC express insulin and leptin receptors.[24,25] Leptin and insulin stimulate POMC and inhibit AgRP expression.[26] GnRH neurons do not express leptin receptor but leptin moderates GnRH function through neuropeptide Y and melanocortin system. GnRH neurons express MC3R and MC4R[27] and melanocortins and NPY can directly modify the activity of GnRH neurons,[28] indicating their role in the central control of reproduction and metabolism. Mice models have suggested that Leptin and Insulin resistance in POMC neurons can lead to obesity, subfertility, sexual dysfunction decreased MSH level.[29]

Testosterone in obesity

Testosterone is present in plasma as free or unbound testosterone, albumin-bound and sex hormone-binding globulin [SHBG] bound. Obesity is associated with a reduction in serum total and free testosterone and SHBG levels, indicating decreased testosterone production.[30] Adipose tissue increases the estrogen levels due to increased aromatase activity which downregulates gondatrophins and decreases testosterone levels.[31] There is also a strong negative relation between BMI and Inhibin Levels.[30] This decrease in testosterone is not followed with a feedback increase in Gonadotrophins indicating a Hypogonadotrophic hypogonadal cycle in obese men. In obesity excess adipose tissue increases the activity of aromatase enzyme, which converts Testosterone into Estradiol. This decreases Luetenising hormone level through a negative feedback mechanism. Obesity leads to reduced testosterone but studies have shown that the decreased testosterone itself can further lead to obesity.[32] Androgen receptor Knock out (ARKO) mice models have shown increased adipocyte numbers also proving that fat is androgen sensitive.[32] Another study of targeted deletion of androgen receptors showed that low testosterone

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can add to the effect of high-fat diet as ARKO mice had more visceral fat deposition.[33] Thus testosterone and obesity affect each other.

Obesity and testicular function

Obese men have decreased testosterone and SHBG levels, the mechanisms of which have been outlined above. Obesity also leads to lipid accumulation and this alters the overall testicular environment.[34] The altered environment affects Leydig cell function. Insulin-like factor 3 (INSL3) produced by the Leydig cell is a marker of its function.[34] Obese men had a significantly lower INSL3 indicating Leydig cell dysfunction in obesity. Similarly, Inhibin B represents Sertoli cell function, which is negatively correlated with BMI. Inhibin is a glycoprotein hormone which negatively effects serum FSH levels. Inhibin levels are low at the time of birth and increase to adult levels by 1st week of birth in males. Thereafter the levels increase to much higher levels than adults by 3-6 months of age and then reaches nadir by 3-6 years and remain low until puberty.[35] During the early post-natal life there is increase in number of sertoli cells[36] as well as changes in number of germ cells.[37] The early activation of the hypothalamic pituitary testicular axis helps in proliferation of sertoli and germ cells. Inhibin B levels in testis are stimulated by FSH and also the inhibin B decreases FSH secretion. The level of Inhibin B is regulated by two factors FSH and ongoing spermatogenesis.[38] One of the studies has shown a strong negative correlation between raised BMI and inhibin levels.[30]

Effect of leptin on testis

Studies by Kus et al.,[39] showed that leptin infusion in mice caused increased testicular weights and diameters of seminiferous tubules compared to those in control mice. Leptin-treated mice showed increased testosterone staining reflecting increased cell activity of leydig cells following administration of leptin.[39] All these findings further prove that testicular function and testosterone synthesis increases after leptin infusion. A study by Martins also proved a similar conclusion that mice lacking leptin receptor were overweight and infertile.[40] Most of the obese individuals develop leptin resistance. The cause of leptin resistance could be impaired leptin transportation across the blood brain barrier.[41] Diet Induced obesity models have also shown location specific resistance to leptin action in hypothalamus, in particular related to its anti-obesity action.[42] Leptin staining in testis of infertile versus fertile man has not been significantly different indicating a neuronal rather than local action of leptin in testis.[43] Studies have shown that excess leptin levels may affect androgen level directly by inhibiting the conversion of 17 hydroxy progesterone to testosterone.[44]

Obesity and insulin resistance

Obesity is a state of Insulin resistance and study have shown that obese men with Insulin resistance have significantly lower testosterone levels than age-matched controls.[45] Insulin-like growth factor is present in testis. Neuron-specific disruption of the Insulin receptor gene NIRKO mice has shown impaired spermatogenesis because of dysregulation of Luteinizing hormone at Hypothalamic level.[46] However, one of the studies has hown contradictory results and proved that NIRKO mice had normal puberty and fertility.[47] Although the action of insulin in neuroendocrine regulation is certain the site can be upstream of GnRH neurons. Insulin resistance decreases SHBG levels and testosterone in the body.[48] Thus Insulin resistance play a key role in reproductive morbidity.

Obesity and liver metabolism

Insulin helps to maintain energy balance by promoting glucose uptake by tissues. In the liver, Insulin inhibits gluconeogenesis and promotes fatty acid synthesis. In the state of obesity, the hepatic insulin resistance leads to lipid accumulation in the liver leading to fatty liver. The hepatic steatosis may also lead to apoptosis, liver fibrosis or even cirrhosis.

Obesity and prostate

Obese men have low serum Prostate-specific antigen (PSA) compared to lean men as shown in studies.[49,50] The reason postulated for the same is low testosterone and increased plasma volume in obese men. The low levels of PSA can make detection of prostate cancer more difficult in obese men. In fact studies have recommended a BMI specific PSA equation.[51] Obesity has also been associated with prostate cancer. The reason of association between obesity and prostate cancer seems to be multifactorial including decreased testosterone, oxidative stress and altered insulin axis.

Obesity and chronic inflammation

The adipocytes secrete Adipokines like Resistin, Leptin, Interleukins (IL-1, IL-6, IL-18), TNF α to name a few. Cytokines like TNFα and Interleukins which are inflammatory are increased in obesity due to increase in adipocytes. The pro-inflammatory cytokines levels are also increased in the serum, testicular tissue and the seminal plasma of obese males.[52] Many inflammatory disease like Rheumatoid arthritis also show decreased testosterone levels. These cytokines also increase the Insulin Resistance. The Pro-inflammatory cytokines have a negative impact on hypothalamic pituitary testicular axis and decreasing the testosterone level further.[53]

Association between BMI and semen analysis

Semen analysis remains the gold standard for evaluation of male fertility. Numerous studies in obese women have shown significant changes like ovulation dysfunction, hormonal disturbance, and impaired fertility.[54]The relation between obesity and semen parameters tends to be multifactorial. One of the possible hypothesis could be altered hypothalamic-pituitary-gonadal axis. Also, Obesity is associated with increases oxidative stress in seminal fluid and chronic stress affecting seminal quality.[55] In a diet-induced obesity model in male mice showed a decrease in motile spermatozoa, increase in intracellular reactive oxygen species and also an increase in sperm DNA damage in the HFD group.[56] Studies have shown a negative correlation between BMI and semen volume, sperm concentration (log), total sperm count (log), vitality, and motility (overall and progressive).[57] Another meta-analysis showed that high BMI decreased sperm quality such as sperm count, concentration, and semen volume rather than sperm motility (overall or progressive).[58] Meta-analysis on Obesity and semen parameters in fertile men by Taha et al showed a significant decrease in sperm motility and sperm normal morphology. Also, a significant increase was seen in seminal sperm DNA fragmentation and seminal reactive oxygen species among obese fertile men.[59] These results were more significant in fertile obese men than in fertile overweight men. Also, weight loss, life style modifications leads to improvement in semen parameters including total sperm count, semen volume testosterone, SHBG and AMH levels.[60] Also sperm membrane constitution is both saturated and unsaturated fatty acids. These fatty acids are important for sperm motility and function. High concentration of Docosahexanoic acid in

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spermatozoa has been associated with greater motility in humans.[61] Raised BMI has shown decreased levels of DHA in sperm which might cause poor motility in obese men.[62]

Obesity and testicular temperature regulation

Spermatogenesis requires a lower temperature as has been known that scrotal temperature is lower than the core body temperature. Mice model of abdominal testes have shown that germ cell loss occurs to heat stress by apoptosis.[63] A similar hypothesis can be put forward for obese men. Obese men have more inner thigh and abdominal fat which is accompanied by a sedentary lifestyle which might lead to elevated scrotal temperature and thus impaired spermatogenesis. Animal studies where the testicular temperature was increased showed increased apoptosis and testis weight was decreased.[64] How heat affects semen parameters is more complex and involves the activation of apoptotic pathways and oxidative stress mechanism.

Obesity and erectile dysfunction

Diet induced obesity models in mice have linked obesity to erectile dysfunction.[65] Various studies have shown that Obesity increases the risk of erectile dysfunction.[66,67] The cause of erectile dysfunction could be low testosterone levels or metabolic abnormalities leading to vascular damage. However waist circumference and lack of physical activity has been proved to be a better predictor of erectile dysfunction than BMI.[68] Infact life style modifications helps to restore obesity associated erectile dysfunction.[69] Weight loss surgeries have shown to reverse the hormonal imbalance and reduce erectile dysfunction.[70]

Conclusion

In summary, male obesity adversely affects the reproductive function. The impact is seen at multiple levels at the Hypothalamic pituitary testicular axis, leptin resistance, Hypothalamic pituitary-adrenal function, Chronic inflammation leading to oxidative stress and hampering the overall environment for spermatogenesis and thus affecting semen parameters. Both the energy homeostasis and reproductive system are also closely interlinked highlighting the role of insulin, adipokines, and melanocortin in the reproductive system.

Limitation

Only articles published in English and till last 20 years were included in the review. The article is an overview of reproductive morbidity in obese men and does not describe details and molecular or genetic levels of dysfunction.

Future direction

Obese male exhibit multiple reproductive alterations. However, there is a need to study the effect of weight loss on the basic pathophysiology in obesity. The time frame for the manifestation of adverse outcome seen in obesity, example effect of acute versus chronic obesity is something that should be further studied. Also the varied effect of childhood obesity versus adult onset obesity should be studied. There is a need to study Obesity related epigenetic modification in sperm. Physically active obese men might have a better testicular function than inactive obese men and there is a need to study the effect of physical activity on testicular function. Obesity associated with comorbid conditions can further affect the semen parameters. Other confounders affecting semen parameters like seasonal variation, job, exposure to heat, radiation exposure need separate models to be studied. Also, there is a need for more human or primate studies to confirm the pathophysiological changes found in lower species.

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Conflicts of interest

The author declares there are no conflicts of interest.

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