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Obesity and Its Impact on Male and Female Fertility

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Abstract

Obesity constitutes a serious health concern as its increasing rapidly worldwide. What is more alarming is that obesity is increasingly now being observed among all age groups in India. Obesity is gateway to many health issues including impairing fertility of both males and females. It has been observed in obese male and female individuals have altered adipokine and other hormonal profile, with poor quality of sperm and oocyte and varied epigenetic modifications of the germ cells. The review focuses on various aspects of how obesity reduces fertility in both the genders. The review also discusses some of the obesity management procedures which thereby also might help in controlling infertility among obese individuals, particularly, how brown adipose tissue (BAT) might be a focus for new therapeutics for obesity by increasing energy expenditure in obese individuals.

Keywords: Obesity; Fertility.

Introduction

Undernourishment a condition that prevailed in the past due to poverty is rapidly replaced by obesity mostly influenced by industrialization, urbanisation and affluence in India. According to the World Health Organization (WHO) statistics, globally one in six adult people suffer from obesity and nearly 2.8 million people die each year due to either overweight or obesity. A recent study showed that the rate of obesity is constantly increasing redundantly and prevalence of overweight (BMI ≥ 25-29.9 kg/m2) and obesity (BMI ≥ 30 kg/m2) is higher among females than males (Indulekha et al., 2015). If persists, obesity can be the path to many associated metabolic risk factors or metabolic syndromes (MetS) such as non-insulin dependent diabetes mellitus (NIDDM), cardiovascular diseases (CVDs) insulin resistance (Reaven et al., 2004).

Indeed, the etiology of obesity is highly complex which includes genetic, physiologic, environmental, psychological, social which interact in varying degrees to promote the development of obesity (Aronne et al., 2009). In accordance to the International Diabetes Federation in 2006, for a person to be diagnosed with metabolic syndrome, the following criteria have been defined: central obesity measured by waist circumference plus two additional factors such as reduced high density lipoprotein (HDL) cholesterol (<40-50 mg/dl) level, raised triglycerides (>150 mg/dl) level, increased blood pressure (>130 mm Hg systolic or >85 mmHg diastolic) or raised level of fasting plasma glucose (>100mg/dl) (Eddy et al., 2008).

Undoubtedly, the end results are that humans have a well-defined biological time interval, restricting fertility and reproduction shorter than the life expectancy. Thus, the price of obesity is represented by a long list of comorbidities along with various social, psychological and demographic problems. This exposes both men and women to a greater risk and impact of negative biological and environmental factors. Hence there is a need for urgent novel methods for new weight-loss treatments.

Effects of Obesity on Males

Studies have shown that males suffering from obesity have decreased plasma concentration of

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testosterone, on account of enhanced conversion to estrogen (Kley et al., 1980). The decrease in testosterone is also due to the decrease in sex hormone-binding globulin, SHBG, which may appear be increased due to insulin resistance. Obese men also exhibit an increase in estradiol, estrone, defective estrogen receptors. Also, the excess accumulation of fatty tissue enveloping the scrotum, suprapubic and thigh regions causes hyperthermia or higher scrotal temperatures leads to oxidative stress to the testicles and further has detrimental effects on spermatogenesis (Setchell, 2009). Such undesired scrotal heating on spermatogenesis and fertility are equally evident in non-human primates. Another interesting study on male aging found that overweight men were more prone for erectile dysfunction regardless if they lost weight during the follow-up (Derby et al., 2000).

Overweight and obese men were found to have a 21.6% (95% CI 4%–39.4%) reduction in their sperm concentration compared with normal-weight men. Using flow cytometry, the chromatin integrity in sperm was evaluated and an increase DNA fragmentation is correlated with infertility (Kort et al., 2006). Interestingly a study showed male mice fed with high fat diet displayed altered acetylation status in late round spermatids. Disruptions to the sperm histone acetylation lead to increased DNA damage in mature sperm and potentially correspond to poor sperm parameters that are observed in obese males (Jenkins et al., 2012).

Adipose tissue in addition to be an important organ maintaining balance in energy homeostasis, it also secretes a huge number of cytokines, known as adipokines, such as leptin, adiponectin, resistin, visfatin, etc. (Rosen and Spiegelman, 2006). In obese men, leptin level increases which has an inhibitory effect on the testosterone production. Studies in rodents showed that leptin concentrations at par with that of obese men directly inhibited the conversion of 17OH-progesterone to testosterone. The presence of leptin has been demonstrated in human male spermatocytes in the testes, increased levels of leptin might disrupt spermatogenesis (Ishikawa et al., 2007).

Effects of Obesity on Females

Females suffering from obesity contribute relatively a long list of metabolic derangements and further consorted with severe reproductive consequences. Evidence suggests excess of body fat is concorded with increased number of polycystic ovarian syndromes (PCOS), miscarriages, macrosomic fetus, pre-eclampsia, infertility and infertility treatment failure, amenorrhea, multiple complications in pregnancy, gestational diabetes and multiple consequences. Studies have showed that onset of obesity and of menstrual irregularities and oligo-anovulation are significantly correlated between adolescent and young women (Pelusi et al., 2003). The fat distribution in the abdomen may have a specific impact on ovulation and fertility.

Obesity plays a distinct pathophysiological role in the development of hyperandrogenism in women with PCOS and these individuals are characterized by blunted responsiveness to pharmacological treatments to induce ovulation, recurrent miscarriages, reduced incidence of pregnancy and frequent early pregnancy loss. Women with PCOS appear to have a greater prevalence of obesity than expected in the general population. An estimated prevalence rate of more than 30% of cases and, in some series, a percentage as high as 75% exists. Several factors are associated with the complex network relating obesity and PCOS. These factors include insulin, the insulin growth- factor system, the opioid system, estrogens and several cytokines, particularly leptin (Sam 2007).

Obesity drastically impacts the quality of oocyte, which implies lower fertilization rates (Shah et al., 2011). A decline in incidence of embryo transfer and decreased number of transferred embryos have been observed in linear association with increasing BMI. Obesity is also associated with a higher risk of obstetric causes of maternal death as well as anaesthesia-related deaths (Ramsay et al., 2006). Pregnant obese women show a series of complications mainly in the third trimester, such as hypertension, preeclampsia, gestational diabetes, urinary tract infection, thromboembolism, operative vaginal deliveries caesarean-section delivery, anaesthetic and surgical complications, fetal macrosomia, preterm labour and delivery, sudden and unexplained intrauterine death, shoulder dystocia, postpartum haemorrhage, postoperative wound infection and endomyometritis in the puerperium (Arabin and Stupin, 2014).

Management of obesity

Obesity is the gateway to several issues particularly affecting both male and female fertility, so if one tries to manage obesity; it might be instrumental in management of infertility among obese infertile people. There are various alternatives to manage obesity and metabolic disorder; however, the most effective would be having a drastic change in lifestyle particularly the eating habits. Walking daily for some time is

considered an effective cardiorespiratory fitness exercise which may drastically improve the metabolic risk profile (Poirier and Després, 2001). Invasive Surgery to reduce weight are effective however, there are reports that such weight loss surgeries are associated with serious complications in 4.1% of patients and a death rate of 0.3%, (Lim et al., 2010).

Non-invasive methods have also been adopted and effective against hyperglycemia to reduce the hepatic glucose through 5′ AMP-activated protein kinase, AMPK activation (Zhou et al., 2001). Although reports exist that these methods might have unacceptable side effects. Glucagon like peptide 1 (GLP-1) analogues which stimulate insulin secretion are used and DPP4-inhibitors that help to prolong GLP-1 action are prescribed without many side effects. Fewer other effective measures are used along with low-calorie intake such as fat absorption blockers, which inhibit the gastric and pancreatic lipases (Curran and Scott, 2004).

New therapeutic methods

There are two main adipose tissue evolved for two different purposes, white adipose tissue (WAT) to survive famine and brown adipose tissue (BAT) to prevent hypothermia (Enerback S, 2010). In addition to these two there is also another intermediate adipose tissue termed beige. Beige adipocytes resemble white adipocytes but possess the classical properties of the brown adipocytes (Whittle et al. 2011; Wu et al. 2012). Studies have quantified BAT oxidative metabolism, glucose and non-esterified fatty acid (NEFA) in 6 healthy human subjects, thus demonstrating unequivocally that BAT contributes to energy expenditure in humans (Ouellet et al., 2012). The presence of the 32 kDa uncoupling protein-1 (UCP-1) in the BAT mitochondria enables heat dissipation thereby resulting in thermogenesis (Nicholls and Locke 1984). During embryonic development, the BAT is formed before other fat depots and is assumed to contain a uniform population of adipocytes. Whereas the beige adipocytes are less clear with respect to its embryonic origin. The browning of the white adipose tissues is often those referred to as ''subcutaneous'' adipose tissue depots. The depots least able to respond are those often referred to as ''visceral''.

Many new therapeutic manipulations of peripheral mechanisms are studied to increase energy expenditure which would be attractive and worthy of focus. Current trends in BAT therapeutics deploy surgically implanting BAT, the augmentation of BAT content and/or enhancement of BAT activity, trans-differentiation of non-BAT progenitors into BAT pre-adipocytes which will increase energy expenditure of obese individuals. Translating the power of BAT into human health appeared much more feasible than reintroducing true BAT into adult men with the concept that certain WAT depots could develop brownish characteristics such as beige, brite, convertible, ectopic, inducible, or recruitable (Schulz et al., 2013). Thus, pragmatically defining browning as any significant increase in UCP1 expression at the mRNA level occurring in white adipose tissue depots (Nedergaard and Cannon, 2014). Numerous transcriptional regulators of brown adipocyte differentiation are currently described in rodents, some revealing promising effects in human models.

A study showed following exercise in both rodents and humans released irisin, a hormone released by muscle, through increased PGC-1α expression. Both through *in vitro* and *in vivo* techniques it was showed that irisinhas a powerful browning effect on certain white adipose tissues (Bostrom et al., 2012). Brown adipocyte stem/progenitor cells, CD34+ in skeletal muscle and human multipotent adipose derived stem cells (hMADs) in subcutaneous tissue in adult humans, serve as novel molecular targets for the development of BAT therapeutics. As evidenced that subcutaneous transplantation of embryonic BAT corrected type 1 diabetes in immune-competent mice by reversal of diabetes symptoms, weight regain and normalization of glucose tolerance also that the mice remained euglycaemic 6-months following the procedure (Gunawardana and Piston 2011).

Also, ghrelin, a adipokine, is secreted by the stomach to increase appetite in the fasted state opposing the actions of leptin. Its central administration results in the suppression of the sympathetic activation of BAT thereby reducing energy expenditure and ablation of the ghrelin receptor results in increased BAT thermogenesis and energy expenditure (Mano-Otagiri et al., 2010). Whether other peripheral hormones and adipokines that modulate feeding and energy expenditure would have any effect of thermogenesis requires further investigation.

Conclusion

Currently there is persuasive evidence suggesting targeting brown adipocytes will yield an effective anti-obesity therapy. Finding hormones and adipokine that regulate metabolism and combining novel therapies that enhance BAT activity with an

appetite-suppressant might provide promising and effective management strategies with respect to obesity thereby curbing the associated metabolic disorders highlighted earlier and improving fertility status.

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