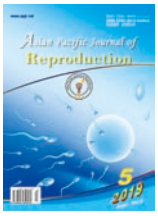

Review Article

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Obestatin in male reproduction and infertility

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ABSTRACT

Obestatin is a 23-amino acid peptide hormone secreted by the stomach and is found in several tissues all over the body, such as the gastric mucosa, spleen, mammary gland, plasma as well as in the testicular Leydig cells. Obestatin seems to operate as part of the integrated gut-brain network acting as an anorectic hormone, reducing food intake and reversing body weight gain. Besides the expressions of obestatin in male reproductive tissues, it is also shown to increase testosterone secretions, thus ameliorating testicular functions. In the present scenario where the increasing prevalence in obesity is considered as one of the major causatives of worldwide declining trend of semen quality, molecules like obestatin playing roles in both metabolic and reproductive functions find importance in management of obesity-induced male infertility or subfertility. The present review article aims to provide updated concepts on obestatin and its mode of actions, and its role in modulation of male reproductive functions.

1. Introduction

The worldwide prevalence of obesity is following a steadily increasing trend that parallels the declining trend in male reproductive functions[1-5]. The World Health Organization reports that 39% of the worldwide adult population is either overweight or obese[6]. Obesity is a complex multifactorial metabolic disorder[7-9] that poses a risk of acquiring several chronic diseases[10]. It affects male reproductive functions leading to impaired spermatogenesis, low sperm count, reduced number of normal motile sperms, increased sperm DNA fragmentation and poor semen quality[11-14].

Management of male infertility in obese men has gained high importance in research. In this regard, obestatin, a 23-amino acid amidated peptide, caught attention for its role in food intake behavior, stomach emptying and reversal of high body weight[15,16]. Its biological activities are thereby opposite to that of ghrelin, even if both are derived from same precursor protein[17]. Obestatin was detected in several tissues throughout the body that includes gastric mucosa, plasma, mammary glands, as well as in the testicular cells[18,19]. Thus, it may also act as local autocrine or paracrine factor besides its endocrine actions. Its expression in the Leydig cells of testes[19], stimulatory effects upon cellular proliferation at the peripubertal phase in male rats and upregulation of testosterone secretion[20-22] indicate its relevance in testicular functions. However, the exact roles of obestatin in regulation of male reproduction are not completely understood. Considering the global declining trend in male fertility parameters[23,24] and the concurrent

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increase in the prevalence of metabolic syndrome, obestatin finds potential applicability in understanding the association of energy balance and reproductive functions. This review article thus aims to present: (a) an overview on obestatin and its mode of actions, and (b) the role of obestatin in modulation of male reproductive functions in normal and obese men. This concise review may provide further insights in the management of obesity induced male infertility or subfertility.

2. Obestatin: Hormone, receptors and physiological functions

Obestatin, as reported by Zhang *et al*[25] is an anorexic hormone that positively influences glucose homeostasis by enhancing the pancreatic β-cell mass, decreasing insulin resistance and associated adipose tissue inflammation[26,27]. Its name is derived from two Latin words 'obedere' meaning to devour and 'statin' meaning to suppress[25]. Studies on human showed predominant obestatin production in the gastrointestinal tract, particularly in the stomach, duodenum, jejunum, and ileum[28]. Apart from being produced in the gastrointestinal tract, it may be also synthesized in the brain, mammary gland as well as in the testicular cells[29]. A single gene code for the common precursor protein for ghrelin and obestatin is called the ghrelin-obestatin preproprotein[25]. Ghrelin is well known for its potent signals for appetite, playing a vital role in energy homeostasis[30,31]. In contrast to ghrelin's appetite and gastrointestinal motility stimulants, obestatin has been documented to decrease food intake, reverse body weight gain, and also to enhance gastric migration[32–34].

Reports suggest that there are numerous metabolic strategies in regulation of functions of adipocytes and glucose metabolism in conditions of obesity[27]. The gene encoding both ghrelin and obestatin may get altered according to the metabolic need of the body, such that alternative insertion may result in its multiple transcript variants, while, antisense transcripts may also occur[35].

The ghrelin gene that also encodes obestatin is located in the short arm of chromosome 3 (3p) in human[33,36]. It comprises of 4 exons leading to a 117-amino acid preprohormone, preproghrelin[37]. According to these studies, preproghrelin hosts the exon 1 encoded preproghrelin signal peptide which is a 28-amino acid ghrelin peptide and exons 2, 3 and 4 encoded C-ghrelin which is a 66-amino acid C-terminal peptide. This C-terminal peptide has been found in the human circulation, but its physiological functions are yet not known. It may reflect alterations in the ghrelin gene encoding a 3-deleted cut C-ghrelin exon only for encoding ghrelin but not for obestatin. Obestatin-23 sequence is the same as residues 76-98 of C-ghrelin, but it is not known whether the obestatin is post-translationally C-gly-related or an alternative gene addition product[37]. It is suggested that obestatin requires additional C-terminal amidation to be biologically active. This 23-amino acid C-terminally mixed peptide is derived from preproghrelin and is attributed to a wide variety of metabolic effects[29].

Most of the studies on obestatin focused on its role in obesity and in regulating energy homeostasis. Obestatin also appears to exert a pleiotropic effect on the cardiovascular system, possibly triggering blood pressure, cardiovascular mechanisms that modulate endothelial function and may be important in determining cardiovascular outcomes of type 2 diabetes[29,38]. The levels of normal physiological obestatin reported in the literature are very variable. Recently it has been shown that obestatin levels in rodents ranged from 1.34 to 2 560.00 pg/mL, whereas the levels reported in humans showed equal variances between 8.400 to 22.077 pg/mL[39].

Obestatin acts through G protein-coated motility receptor of the ghrelin receptor and growth hormone secretagogue receptor-1 activation[25,40]. The growth hormone secretagogue receptor is expressed in α, β and δ cells of pancreatic islets[41,42]. It has been proposed that obestatin works through two functional receptors, G protein-coated motility receptor-39 and Glucagon-like peptide 1 receptors[25,41]. Both these G protein-dependent receptors were found to correlate with the metabolic functions of obestatin[29,37,43–45]. However, the understanding of the exact intracellular mechanism of action of obestatin *via* its receptors needs further interventions.

3. Obestatin and regulation of obesity

As obesity is usually characterized by abnormal excessive fat deposits which are detrimental to health, many promising researches have been conducted on the appetite control mechanism and its regulating factors. Recent research trend is inclined towards endogenous appetite regulatory peptides, such as obestatin, which was found in mammalian stomach and also in some other vital organs and tissues[46]. In humans, the level of obestatin production depends on physiological and metabolic status of the subjects, varying greatly in the ones with obesity or anorexia from that in the control subjects[47–49].

As discussed earlier, obestatin, is encoded by the same gene as that for ghrelin and both these hormones are produced from a common precursor – preproghrelin, having counteracting effects on food intake[50,51]. Obestatin treatments on rats showed suppressed food intake behavior[25,44,52], inhibition of jejunal contractions and reduction in body weight[25,52]. Obestatin has also been shown to regulate pancreatic β-cell survival and insulin secretion[46]. It has also been noted that obestatin levels were reduced in morbidly obese subjects who underwent bariatric surgery[53]. A study conducted on women showed that lower plasma obestatin levels were found in obese subjects compared with subjects with normal weight. These findings agree partly with the study by Guo *et al*[54], in which preprandial obestatin levels were found lower in obese men and women. Studies have further shown that obestatin treatment influences phospholipid turnover and impacts lipid homeostasis,

while giving persuading proof that obestatin might act to improve diet-induced restrictions in lipid digestion, and it might impact upon steroid, bile acid and glutathione digestion.

Although evidences showed that obestatin might be involved in the regulation of energy balance and body weight, there are conflicts in the exact roles of obestatin in obesity[55]. Even though several studies have witnessed the inhibitory effects of obestatin on food intake, obesity and gastrointestinal motility, a consensus is not reached yet[56–59].

4. Obestatin and male reproductive functions

Hormones associated with the hypothalamus-pituitary-gonadal axis along with its crosstalks with other axes regulate the male reproductive functions[14]. Research suggests that the factors associated with growth and body weight homeostasis, also possess various roles in the regulation of reproductive function[60–63]. Obestatin has also been claimed to play such dual roles mediating both energy homeostasis and testicular functions[64,65]. In adult male rats, it was observed that a single intravenous injection of obestatin could trigger testosterone secretion and its chronic infusion in prepubertal rats significantly increased both testosterone production and spermatogenesis[20,22]. It also significantly reversed diabetes mediated compromised male fertility parameters, such as epididymal sperm count, sperm motility, testicular enzyme activities, and sperm morphology in rats. Moreover, obestatin may have protective role against diabetes-induced testicular dysfunctions, owing to its antioxidant properties[66]. In this regard, it may be put forth that obestatin plays essential role in resisting as well as reversing metabolic disorder-induced male reproductive impairments. These attribute to the integration of its functions in metabolic homeostasis with maintenance of testicular functions[65,67].

5. Obestatin and semen quality

The effects of obestatin on reproductive functions are not well defined but it is presumed to improve testicular functions in obese subjects[66,68]. It is generally thought that ghrelin and obestatin, which control metabolism, regulate cellular metabolic activations in the reproductive system[19]. Both obestatin and ghrelin levels were found to be higher in semen than in serum[66], portraying a linear correlation between serum and semen levels of ghrelin and obestatin. In male rats, obestatin has been shown to be expressed in the testes, especially in the Leydig cells[19]. Moretti *et al* have also reported immunoreactivity for obestatin in the spermatozoa, seminal vesicles and prostate[68]. Obestatin levels in semen showed positive correlation with essential semen parameters such as the sperm motility and sperm concentration[65,66,69,70]. In obese mice, immunoreactivity of both ghrelin and obestatin were shown to decrease in testes. However, in a study conducted by El-Damarawi *et al*, exogenously administered obestatin and L-carnitine decreased obesity-related parameters and increased testosterone levels and weight reduction have been observed[65]. They also showed increase in primary and secondary spermatocytes, spermatids and Leydig cell populations after administration of obestatin[22].

Thus, it may be suggested that obestatin may improve semen quality by ameliorating spermatogenesis and by inducing proliferation of testicular cells like the Leydig cells, thereby increasing the possibility of higher rate of steroidogenesis. Moreover, its possible influence on the male accessory reproductive glands may suggest its contribution in the secretion of seminal plasma. These studies indicate that obestatin may be a potential modulator in the management of obesity-induced male infertility or subfertility. However, given the inadequate number of studies, the physiological roles of seminal obestatin remain obscure.

6. Conclusions

The present review article has reviewed the most updated available information and presented a concise concept on obestatin and its role in male reproductive functions. It is clear from the above discussions that obestatin plays vital roles both in reversing body weight and management of obesity, as well as in ameliorating male reproductive functions. Recent research trend shows an increasing interest in exploring the association of metabolic disorders with reproductive impairments. In this context, obestatin appears to be a potential hormone that may be explored to ameliorate obesity-induced male infertility or subfertility.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

[1] Sengupta P, Dutta S, Krajewska-Kulak E. The disappearing sperms: Analysis of reports published between 1980 and 2015. *Am J Men's Health* 2017; **11**(4): 1279-1304.

[2] Sengupta P, Borges Jr E, Dutta S, Krajewska-Kulak E. Decline in sperm count in European men during the past 50 years. *Hum Exp Toxicol* 2018; **37**(3): 247-255.

[3] Sengupta P, Nwagha U, Dutta S, Krajewska-Kulak E, Izuka E. Evidence for decreasing sperm count in African population from 1965 to 2015. *Afr Health Sci* 2017; **17**(2): 418-427.

[4] Sengupta P. Reviewing reports of semen volume and male aging of last 33 years: From 1980 through 2013. *Asian Pac J Reprod* 2015; **4**(3): 242-246.

[5] Sengupta P, Dutta S, Tusimin MB, Irez T, Krajewska-Kulak E. Sperm

counts in Asian men: Reviewing the trend of past 50 years. *Asian Pac J Reprod* 2018; **7**(2): 87-92.

[6] World Health Organization. *Obesity and overweigh*t. Geneva: World Health Organization; 2018.

[7] Barnes AS. The epidemic of obesity and diabetes: Trends and treatments. *Texas Heart Inst J* 2011; **38**(2): 142.

[8] Dutta S, Agarwal A. Obesity. In: Agarwal A, Parekattil S, Esteves S. (eds). *Male infertility: Contemporary clinical approaches, andrology, ART and antioxidants*. New York: Springer Nature; 2019.

[9] Dutta S, Biswas A, Sengupta P. Obesity, endocrine disruption and male infertility. *Asian Pac J Reprod* 2019; **8**(5): 195-202.

[10]World Health Organization. *Obesity: Preventing and managing the global epidemic*. Geneva: World Health Organization; 2000.

[11]Du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A. The effect of obesity on sperm disorders and male infertility. *Nat Rev Urol* 2010; **7**(3): 153.

[12]Hammoud AO, Meikle AW, Reis LO, Gibson M, Peterson CM, Carrell DT. (eds). *Obesity and male infertility: A practical approach*. New York: Thieme Medical Publishers; 2012.

[13]Katib A. Mechanisms linking obesity to male infertility. *Centr Eur J Urol* 2015; **68**(1): 79.

[14]Sengupta P, Arafa M. Hormonal regulation of spermatogenesis. In: Singh R. (ed.). *Molecular signaling in spermatogenesis and male infertility*. London: CRC Press; 2019.

[15]Ren AJ, Guo ZF, Wang YK, Lin L, Zheng X, Yuan WJ. Obestatin, obesity and diabetes. *Peptides* 2009; **30**(2): 439-444.

[16]Lagaud GJ, Young A, Acena A, Morton MF, Barrett TD, Shankley NP. Obestatin reduces food intake and suppresses body weight gain in rodents. *Biochem Biophys Res Comm* 2007; **357**(1): 264-269.

[17]Fujimiya M, Asakawa A, Ataka K, Chen CY, Kato I, Inui A. Ghrelin, des-acyl ghrelin, and obestatin: Regulatory roles on the gastrointestinal motility. *Int J Peptides* 2010; **2010**: 1-10.

[18]Subasinghage AP, Green BD, Flatt PR, Irwin N, Hewage CM. Metabolic and structural properties of human obestatin {1–23} and two fragment peptides. *Peptides* 2010; **31**(9): 1697-1705.

[19]Dun SL, Brailoiu GC, Brailoiu E, Yang J, Chang JK, Dun NJ. Distribution and biological activity of obestatin in the rat. *J Endocrinol* 2006; **191**(2): 481-489.

[20]Hizbullah SJ, Ahmed S. Obestatin induces testosterone secretion from rat testis *in vitro*. *Afr J Biotechnol* 2011; **10**(19): 3821-3928.

[21]Jahan S, Ahmed S, Taqvim N. Obestatin induces testosterone but not prolactin secretion in male sprague dawley rats. *Pakistan J Zool* 2010; **42**(6): 836-839.

[22]Jahan S, Sidrat T, Ahmed S, Wazir H, Ullah K. Effect of obestatin on morphometry of testes and testosterone secretion in male rats. *Afr J Biotechnol* 2011; **10**(39): 7717-7722.

[23]Sengupta P. Recent trends in male reproductive health problems. *Asian J Pharm Clin Res* 2014; **7**(2): 1-5.

[24]Sengupta P. Current trends of male reproductive health disorders and the changing semen quality. *Int J Prev Med* 2014; **5**(1): 1.

[25]Zhang JV, Ren PG, Avsian-Kretchmer O, Luo CW, Rauch R, Klein C, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. *Science* 2005; **310**(5750): 996-999.

[26]Granata R, Gallo D, Luque RM, Baragli A, Scarlatti F, Grande C, et al. Obestatin regulates adipocyte function and protects against diet-induced insulin resistance and inflammation. *FASEB J* 2012; **26**(8): 3393-3411.

[27]Gesmundo I, Gallo D, Favaro E, Ghigo E, Granata R. Obestatin: A new metabolic player in the pancreas and white adipose tissue. *IUBMB Life* 2013; **65**(12): 976-982.

[28]Catalán V, Gómez-Ambrosi J, Rotellar F, Silva C, Gil MJ, Rodriguez A, et al. The obestatin receptor (GPR39) is expressed in human adipose tissue and is down-regulated in obesity-associated type 2 diabetes mellitus. *Clin Endocrinol* 2007; **66**(4): 598-601.

[29]Green BD, Grieve DJ. Biochemical properties and biological actions of obestatin and its relevence in type 2 diabetes. *Peptides* 2018; **100**: 249-259.

[30]Moechars D, Depoortere I, Moreaux B, De Smet B, Goris I, Hoskens L, et al. Altered gastrointestinal and metabolic function in the GPR39-obestatin receptor–knockout mouse. *Gastroenterology* 2006; **131**(4): 1131-1141.

[31]Ren AJ, Guo ZF, Wang YK, Wang LG, Wang WZ, Lin L, et al. Inhibitory effect of obestatin on glucose-induced insulin secretion in rats. *Biochem Biophys Res Comm* 2008; **369**(3): 969-972.

[32]Scrima M, Campiglia P, Esposito C, Gomez-Monterrey I, Novellino E, D'Ursi AM. Obestatin conformational features: A strategy to unveil obestatin's biological role? *Biochem Biophys Res Comm* 2007; **363**(3): 500-505.

[33]Chen C, Chien E, Chang F, Lu C, Luo J, Lee S. Impacts of peripheral obestatin on colonic motility and secretion in conscious fed rats. *Peptides* 2008; **29**(9): 1603-1608.

[34]Grande C, Gesmundo I, Settanni F, Taliano M, Gallo D, Gargantini E, et al. Obestatin enhances *in vitro* generation of pancreatic islets through regulation of developmental pathways. *PLoS One* 2013; **8**(5): e64374.

[35]Liu Y, Liu Y, Li G, Chen Z, Gu G. Ghrelin protects the myocardium with hypoxia/reoxygenation treatment through upregulating the expression of growth hormone, growth hormone secretagogue receptor and insulin-like growth factor-1, and promoting the phosphorylation of protein kinase B. *Int J Mol Med* 2018; **42**(6): 3037-3046.

[36]Ren G, He Z, Cong P, Chen H, Guo Y, Yu J, et al. Peripheral administration of TAT-obestatin can influence the expression of liporegulatory genes but fails to affect food intake in mice. *Peptides* 2013; **42**: 8-14.

[37]Epelbaum J, Bedjaoui N, Dardennes R, Feng DD, Gardette R, Grouselle D, et al. Role of the ghrelin/obestatin balance in the regulation of neuroendocrine circuits controlling body composition and energy homeostasis. *Mol Cell Endocrinol* 2010; **314**(2): 244-247.

[38]Gao XY, Kuang HY, Liu XM, Wang XY, Pan YH, Ma XX. Decreased obestatin in plasma in metabolically obese, normal-weight men with normal glucose tolerance. *Diab Res Clin Prac* 2008; **79**(1): e5-e6.

[39]Nogueiras R, Pfluger P, Tovar S, Arnold M, Mitchell S, Morris A, et al. Effects of obestatin on energy balance and growth hormone secretion in rodents. *Endocrinology* 2007; **148**(1): 21-26.

[40]Schinzari F, Veneziani A, Mores N, Barini A, Di Daniele N, Cardillo C, et al. Vascular effects of obestatin in lean and obese subjects. *Diabetes* 2017; **66**(5): 1214-1221.

[41]Granata R, Settanni F, Gallo D, Trovato L, Biancone L, Cantaluppi V, et al. Obestatin promotes survival of pancreatic β-cells and human islets and induces expression of genes involved in the regulation of β-cell mass and function. *Diabetes* 2008; **57**(4): 967-979.

[42]Pradhan G, Wu CS, Lee JH, Kanikarla P, Guo S, Yechoor VK, et al. Obestatin stimulates glucose-induced insulin secretion through ghrelin receptor GHS-R. *Sci Rep* 2017; **7**(1): 979.

[43]Pazos Y, Alvarez CJ, Camiña JP, Casanueva FF. Stimulation of extracellular signal-regulated kinases and proliferation in the human gastric cancer cells KATO-[[[by obestatin. *Growth Fact* 2007; **25**(6): 373-381.

[44]Zhang JV, Jahr H, Luo CW, Klein C, Van Kolen K, Ver Donck L, et al. Obestatin induction of early-response gene expression in gastrointestinal and adipose tissues and the mediatory role of G protein-coupled receptor, GPR39. *Mol Endocrinol* 2008; **22**(6): 1464-1475.

[45]McKee KK, Tan CP, Palyha OC, Liu J, Feighner SD, Hreniuk DL, et al. Cloning and characterization of two human G protein-coupled receptor genes (GPR38 and GPR39) related to the growth hormone secretagogue and neurotensin receptors. *Genomics* 1997; **46**(3): 426-434.

[46]Khirazova E, Motorykina E, Maslova M, Maklakova A, Graf A, Sokolova N, et al. Effect of chronic administration of obestatin and its fragment FNAP-NH 2 on behavioral activity and nociceptive threshold in rats with normal and excess body weight. *Bull Exp Biol Med* 2017; **163**(3): 293-295.

[47]Aydin S, Ozkan Y, Erman F, Gurates B, Kilic N, Colak R, et al. Presence of obestatin in breast milk: relationship among obestatin, ghrelin, and leptin in lactating women. *Nutrition* 2008; **24**(7-8): 689-693.

[48]Bang AS, Soule SG, Yandle TG, Richards AM, Pemberton CJ. Characterisation of proghrelin peptides in mammalian tissue and plasma. *J Endocrinol* 2007; **192**(2): 313-323.

[49]Zamrazilová H, Hainer V, Sedláčková D, Papežová H, Kunešová M, Bellisle F, et al. Plasma obestatin levels in normal weight, obese and anorectic women. *Physiol Res* 2008; 57: S49-S55

[50]Monteleone P, Serritella C, Martiadis V, Scognamiglio P, Maj M. Plasma obestatin, ghrelin, and ghrelin/obestatin ratio are increased in underweight patients with anorexia nervosa but not in symptomatic patients with bulimia nervosa. *J Clin Endocrinol Metab* 2008; **93**(11): 4418-4421.

[51]Dutta S, Biswas A, Sengupta P, Nwagha U. Ghrelin and male reproduction. *Asian Pac J Reprod* 2019; **8**(5): 227-232.

[52]Bresciani E, Rapetti D, Dona F, Bulgarelli I, Tamiazzo L, Locatelli V, et al. Obestatin inhibits feeding but does not modulate GH and corticosterone secretion in the rat. *J Endocrinol Invest* 2006; **29**(8): RC16-RC18.

[53]Haider DG, Schindler K, Prager G, Bohdjalian A, Luger A, Wolzt M, et al. Serum retinol-binding protein 4 is reduced after weight loss in morbidly obese subjects. *J Clin Endocrinol Metab* 2007; **92**(3): 1168-1171.

[54]Guo ZF, Zheng X, Qin YW, Hu JQ, Chen SP, Zhang Z. Circulating preprandial ghrelin to obestatin ratio is increased in human obesity. *J Clin Endocrinol Metab* 2007; **92**(5): 1875-1880.

[55]Qi X, Li L, Yang G, Liu J, Li K, Tang Y, et al. Circulating obestatin levels in normal subjects and in patients with impaired glucose regulation and type 2 diabetes mellitus. *Clin Endocrinol* 2007; **66**(4): 593-597.

[56]Gourcerol G, St-Pierre D, Tache Y. Lack of obestatin effects on food intake: should obestatin be renamed ghrelin-associated peptide (GAP)? *Regul Peptides* 2007; **141**(1-3): 1-7.

[57]De Smet B, Thijs T, Peeters T, Depoortere I. Effect of peripheral obestatin on gastric emptying and intestinal contractility in rodents. *Neurogastroenterol Motil* 2007; **19**(3): 211-217.

[58]Tremblay F, Perreault M, Klaman LD, Tobin JF, Smith E, Gimeno RE. Normal food intake and body weight in mice lacking the G protein-coupled receptor GPR39. *Endocrinology* 2007; **148**(2): 501-506.

[59]Dutta S, Sengupta P, Biswas A. Adiponectin in male reproduction and infertility. *Asian Pac J Reprod* 2019; **8**(5): 244-250.

[60]Caminos J, Seoane L, Tovar S, Casanueva F, Dieguez C. Influence of thyroid status and growth hormone deficiency on ghrelin. *Eur J Endocrinol* 2002; **147**(1): 159-163.

[61]Krajewska-Kulak E, Sengupta P. Thyroid function in male infertility. *Frontiers in endocrinology* 2013; **4**: 174.

[62]Sengupta P, Dutta S. Thyroid Disorders and Semen Quality. *Biomed Pharmacol J* 2018; **11**(1): 01-10.

[63]Alahmar A, Sengupta P, Dutta S. Thyroid hormones in male reproduction and infertility *Asian Pac J Reprod* 2019; **8**(5): 203-210.

[64]Catak Z, Aydin S, Sahin İ, Kuloglu T, Aksoy A, Dagli AF. Regulatory neuropeptides (ghrelin, obestatin and nesfatin-1) levels in serum and reproductive tissues of female and male rats with fructose-induced metabolic syndrome. *Neuropeptides* 2014; **48**(3): 167-177.

[65]El-Damarawi MA, Salama ME. Obestatin and L-carnitine as a defensive strategy against fertility disorders induced by obesity in male rats. *Tanta Med J* 2014; **42**(3): 103.

[66]Moretti E, Collodel G, Iacoponi F, Geminiani M, Pascarelli NA, Campagna S, et al. Detection of obestatin in seminal plasma and its relationship with ghrelin and semen parameters. *Fertil Steril* 2011; **95**(7): 2303-2309.

[67]Latif N, Hussain MM, Khan MA. Effect of obestatin on glucose homeostasis, insulin resistance and serum insulin levels in type 2 diabetic rats. *Pakistan Arm Forces Med J* 2018; **68**(4): 998-1002.

[68]Moretti E, Vindigni C, Tripodi S, Mazzi L, Nuti R, Figura N, et al. Immunolocalisation of ghrelin and obestatin in human testis, seminal vesicles, prostate and spermatozoa. *Andrologia* 2014; **46**(9): 979-985.

[69]Łukaszyk A, Kotwicka M, Jankowska A, Kasprzak A, Ruci ski M, Sterzy ska K, et al. Expression of ghrelin receptor (GHSR-1a) in rat epididymal spermatozoa and the effects of its activation. *Reprod Biol* 2012; **12**(3): 293-300.

[70]Kheradmand A, Alirezaei M, Asadian P, Rafiei Alavi E, Joorabi S. Antioxidant enzyme activity and MDA level in the rat testis following chronic administration of ghrelin. *Andrologia* 2009; **41**(6): 335-340.