IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 3 Ver. VIII (Mar. 2016), PP 63-67
www.iosrjournals.org

Effect Of Ghrelin, Obestatin Levels And The Ghrelin/Obestatin Ratio In Polycysticovary Syndrome

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Abstract:
Background: *Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among females. Central obesity has a close relationship with an altered secretion of some adipocytokines*
Aim Of Study: *investigate the relationship of Ghrelin and Obestatin with their body mass index and fasting insulin values in overweight females with PCOS.*
Subjects And Methods:*twenty four overweight females with PCOS age ranged between (20-45) years with (25) normal weight healthy female with age matched have been included in this study as a control group. BMI and WCwere done for patients and controls as anthropometrical tests, while FSG was measured using spectrophotometric technique, but each of Ghrelin,obestatin and fasting insulin were measured using ELISA test.*
Results: *This study showed a significant decline in Ghrelin, Obestatin in patients with PCOS compared with controls, while BMI, WC, fasting Insulin, Ghrelin/Obestatin ratio were significantly higher in patients than that in control group.*
Conclusion: *Over weight patients with PCOS were at a high risk of the metabolic syndrome and accordingly Ghrelin and Obestatin can be used as a good predictor for PCOS overweight females.*

I. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among females. PCOS has a diverse range of causes that are not entirely understood, but there is strong evidence that it is largely a genetic disease.(1, 2)

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age (approximately 12 to 45 years old). It is thought to be one of the leading causes of female subfertility (3), and the most frequent endocrine problem in women of reproductive age.Finding that the ovaries appear polycystic on ultrasound is common, but it is not an absolute requirement in all definitions of the disorder.(4)

The most common immediate symptoms are anovulation, excess androgenichormones, and insulin resistance. Anovulation results in irregular menstruation,amenorrhea, and ovulation-related infertility. Hormone imbalance generally causesacne and hirsutism. Insulin resistance in PCOS is associated with obesity, Type 2 diabetes, and high cholesterol levels.(5)The symptoms and severity of the syndrome vary greatly among affected women.

Adiposity is observed in PCOS patients and plays an important role in their metabolic phenotype through the production of various adipocyte-derived cytokines and proteins known as adipokiens. Central obesity has a close relationship with the altered secretion of some adipocytokines. Production of adipocytokines affects insulin sensitivity and is a predictor of metabolic syndrome.(6)

Ghrelinis a peptide hormone produced by ghrelin cells in the gastrointestinal tract(7) which acts as aneuropeptide in the central nervous system.(8) Beyond regulating hunger, ghrelin also plays a significant role in regulationand distribution the rate of use of energy by complex mechanisms for example energy homeostasis.(9)

When the stomach is empty ghrelin is secreted, and when it is stretched secretion will stop. It acts on hypothalamic brain cells both to increase hunger, and to increase gastric acid secretion and gastrointestinal motility to prepare the body for food intake.The receptor for ghrelin is found on the same cells in the brain as the receptor for leptin, the satiety hormone that has opposite effects from ghrelin. (10)

Ghrelin secretion may be affected by adiposity through insulin and/or glucose metabolism. Studies performed in humans demonstrated that i.v. administration of insulin induces a fall in ghrelin levels, this decline in ghrelin concentrations, in turn, is related to insulin sensitivity. The ghrelin receptor can also be found in ovarian issue, thus suggesting a possible reproductive function for ghrelin. (11)

Obestatin: Obestatin is a 23-amino acid amidatedpeptide encoded by the ghrelin gene that isalso released from the stomach. It has beenshown to interact with the orphan receptorG-protein-coupled receptor 39, and tooppose the stimulatory effect of ghrelin onfood intake and gastrointestinal function.Studies in humans have shownthat blood obestatin levels are significantlylower in obese subjects and correlate negativelywith body mass index.(12)

In addition, obestatinhas been shown to be positively correlatedwith ghrelin (13, 14);this suggests that levels ofboth obestatin and ghrelin may be altered inobesity and insulin resistance.

II. Aim of this study

The aim of the present study was to measure fastingplasma ghrelin and obestatin concentrations in obesePCOS females and control subjects and to investigate their relationshipwith their body mass index and fasting insulin values.

III. Subjects And Methods:-

This study had included twenty four (24)overweight femaleswith PCOS age ranged between (20-45) years with twenty five(25)normal weight healthyfemale withage matched have beenincluded in this studyas a control group whowere attendingthe out patients consultation clinic of Gynecology inBaghdadTeaching Hospital /Medical City, in a period from October 2014– march 2015.

-All patients and controls underwent complete general questionnaire. -Patients with suspected thyroid function disease were excluded from the study.

-Body mass index (BMI) and waist circumference (WC) were done for patients and controls as anthropometrical tests, while fasting serum glucose (FSG)measured using spectrophotometric technique.

-Each serum sample was analyzed for ghrelin hormone, obestatin hormone and fasting insulin using enzyme linked immune sorbent assay (ELISA).

IV. Statistical Analyses

Descriptive statistics for all data of each set were expressed as mean ± SD and the percent of abnormal value in any test was calculated as above or below the mean ± SD of the normal value for the matched control group, were compared using independent sample (t)test $p<0.05$ were considered statistically significant.(15)

The overall predictive values for the results in the studied groups were performed according to program of office xp.

V. Results

Table (1):- Mean ± SD of all studied parameters in patients and control group.

Studied parameters	Patients (no=24)	Control (no=25)	P value
	Mean ± SD	**Mean ± SD**	
Body weight (kg**)**	128.9± 32.5	57.67±7.05	0.001(S)
BMII(kg/m^2)	9.09 ±29.48	2.49 ±21.71	0.001(S)
WC (cm**)**	103.90± 9.87	79.56± 5.20	0.002(S)
F.S.G. (mg/dl)	108.2 ± 26.3	88.01 ± 8.62	0.08(NS)
Ghrelin (pg/ml)	42.5±468	36,2±570.1	0.003(S)
Obestatin(pg/ml)	9.35±91.66	210.7 ± 56.0	0.001(S)
Ghrelin/Obestatin ratio	0.573±5.148	0.816±2.900	0.001(S)
Insulin (MU/ml)	28.36± 2.27	6.324 ± 0.938	0.003(S)

Note:S: significant.NS: non-significant.

Results obtained in the present study showed that the serum levels of Ghrelin, Obestatinwere significantly lower in patients with polycystic ovary than in healthy controls. While body weight, BMI, WC, fasting Insulin and Ghrelin \ Obestatine ratiowere significantly higher in patients with polycystic ovary than in healthy controls, as they shown in table (1).

Serum Ghrelin level and serum Obestatinwere negatively correlated with BMI in females with PCOSas they shown in figure(1&2).

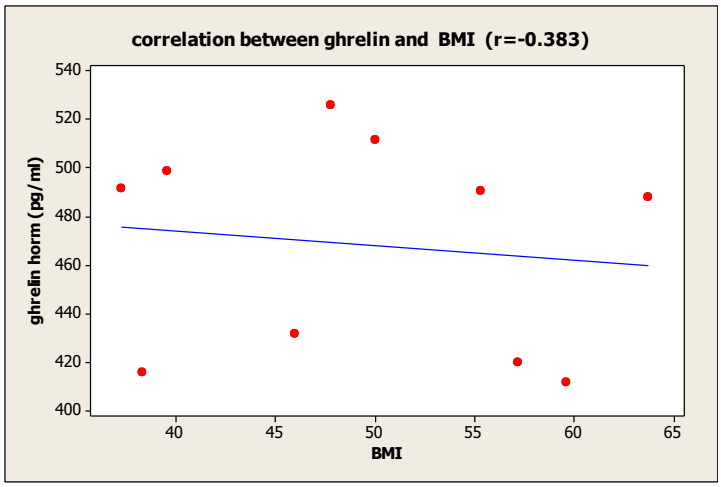

Fig (1): Correlation between ghrelin and BMI in PCOS.

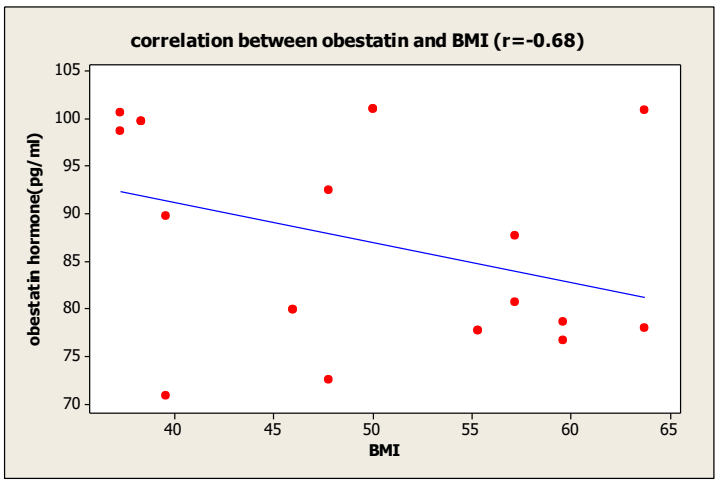

Fig (2): Correlation between Obestatin and BMI in PCOS.

In addition serum Ghrelin and Obestatin showed an inverse correlation with fasting serum Insulin in patients with PCOS, as they shown in figure (3&4).

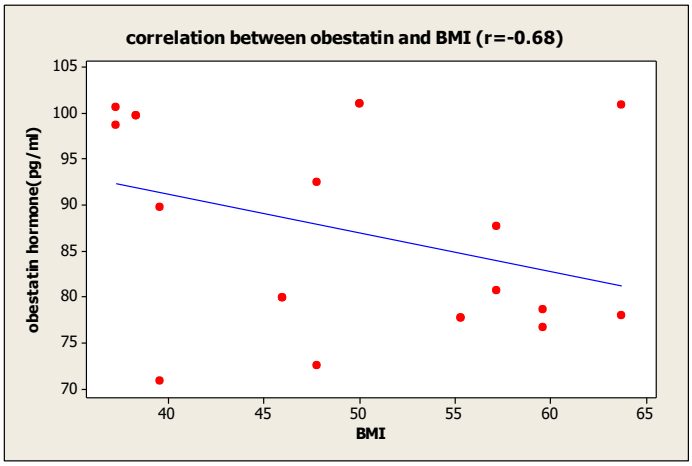

Fig (3): Correlation between serum Ghrelin and fasting Insulin values in PCOS.

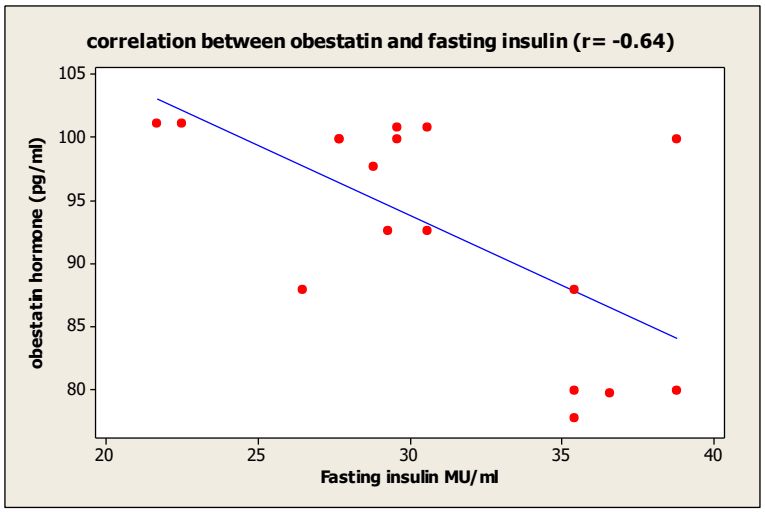

Fig (4): Correlation between serum Obestatin and fasting Insulin values in PCOS.

VI. Discussion

Obesity has become a major public health problem throughoutthe world and at least one-third of Arabs are obese, and thisfigure is rising steadily despite increased interest in fitness.Excess fat accumulation promotes the developmentof insulin resistance, glucose intolerance and type 2 diabetesmellitus.(16)A result obtained in the present study was found a highly significant decreasein Ghrelin level in PCOS women than the control group with negative correlation betweenGhrelin and BMI. Although 21% of the obese subjects werenon-insulin resistance, one cannot exclude the theory thatobesity is associated with hyperinsulinemia and insulin resistance.

Supporting the hypothesis of a negative associationbetween Ghrelin and risk factors of the metabolic syndrome, it's found that there isa significantly inverse correlation between Ghrelin and Fasting Insulin in PCOS patients.

Mitkovet al.(17),Glintborget al.(18), and Kamal et al.(19)published that serumghrelin concentration was lower inthe PCOS group than in healthy controls, while Waskoet al.(20) have reported elevatedlevels of plasma ghrelin in PCOS patientscompared to healthy controls. This discrepancy ofresults may be explained by confounding factors,such as body weight, fat mass, age, hormonal status,and severity of disease.On the other hand, Daghestaniet al. showed a significant inverse relationshipbetween ghrelin and BMI in PCOS,it has been shown that ghrelin administration tohealthy humans at pharmacological doses reducesinsulin secretion, and conversely, insulin administrationat high doses is capable of reducingghrelin secretion. (21) In addition, to a negative correlation between Ghrelin and fasting Insulin hormone in females with PCOS which was conducted by Stępień and his co-workers.(22)

Extensive research on ghrelin has produced evidence that this peptide may have important positive effects on feeding, since exogenous ghrelin administration stimulates appetite and food intake in both rodents and humans. In addition, there is evidence that ghrelin reduces energy expenditure fat catabolism, and lipolysis, and may promote adipogenesis. These findings contrast with the negative correlation between ghrelin levels and BMI. (23)

This study also found that serum levels of obestatin hormone were significantly lower in females with PCOS than in healthy control group which was agreed with Taskin MIet al. who demonstrated that serum obestatin levels were significantly lower in the obese PCOS group than they were in the non-obese and control groups ($p<0.001$). (24)

Obestatin levels were significantly reducedsuggesting that the secretion of the Ghrelin and Obestatin isregulated in an opposing manner by the nutritionalstatus. These findings suggest that obestatincould modulate endogenous Ghrelin actions, andhave shown that obestatin mayinhibit jejunal activity and may suppress gastricemptying activity. (25)

This study showed an inverse relationship between Obestatin with BMI and with fasting Insulin which was disagreed byYildiz Get al,who published that there was no correlation between obestatin levels and homeostasis model assessment-insulin resistance or BMIwhich suggest that distinct mechanisms play roles in the regulation of obestatin levels in case of high BMI. (25)

Changes incirculating ghrelin and obestatin levels may representadaptive modifications to obesity development, ratherthan primary defects, and that their alteration incirculating blood levels may reflect an imbalance ofregulatory factors or mechanisms responsible, in turn,for their metabolic processes and action(26).

VII. Conclusion

Polycystic ovary syndrome is a complex disorder, inwhich multiple genetic, metabolic and hormonal controlsfail to interact properly and produce the hallmark symptomsof the disease. Obese PCOS patients demonstrated significantlylower Ghrelin and Obestatinlevels than that of controls, thus suggesting thissubgroup of patients to be at high risk for the metabolic syndromeand accordingly Ghrelin and Obestatin can be used as a good predictor forPCOSoverweight females.

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