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Ghrelin and Insulin Resistance in a Sample of Iraqi Women with Polycystic Ovary Syndrome

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Abstract

Background Polycystic ovary syndrome is associated with adiposity and metabolic changes predisposing to insulin resistance and diabetes mellitus. Ghrelin is an appetite-stimulating hormone, which acts through its receptor on the hypothalamus to regulate energy balance and thus plays a major role in the etiology of metabolic diseases.

Objective To investigate the relation between ghrelin hormone and insulin resistance in patients with polycystic ovary syndrome.

Methods Thirty nine women with polycystic ovary syndrome and 30 healthy controls were examined. Fasting ghrelin, insulin, glucose, lipid profile concentrations were determined. Insulin resistance indexes were calculated (HOMA-IR and QUICKI-IR indexes).

Results Serum ghrelin concentration was significantly lower in polycystic ovary syndrome patients than control subjects (235 ± 17.36 pg/ml *Vs* 489.7 ± 53.4 pg/ml). Insulin resistance and BMI were significantly higher in polycystic ovary syndrome than control group.

Conclusion Ghrelin hormone may be used as a new additional marker in the diagnosis of polycystic ovary syndrome. Hyperinsulinaemia and hyperleptinemia are associated features in polycystic ovary syndrome.

Keywords Ghrelin, Obesity, Polycystic ovarian syndrome (PCOS), Body mass index (BMI), Insulin resistance

List of Abbreviation: PCOS = polycystic ovary syndrome, DM = diabetes mellitus, HOMA-IR = Homeostatic Model Assessment of Insulin Resistance, TG = triglyceride, VLDL-C = very low density lipoprotein, HDL-C = high density lipoprotein, BMI = Body mass index, LH = luteinizing hormone, FSH = follicle stimulating hormone

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age with a reported prevalence up to 12% [(1)]. It is a complex multifactorial genetic disorder with dysregulated steroidogenesis [(2)]. The disease is characterized by chronic anovulation, functional hyper-androgenism and polycystic ovaries on ultrasound examination [(3)]. In women with PCOS, the presence of hyperinsulinaemia, dyslipidemia and/or hypertension is associated with obesity. The obesity and PCOS place this group of women at high risk of developing adverse metabolic profiles including insulin resistance [(4)]. Insulin resistance is a metabolic disorder caused by the impairment of insulin function in inducing glucose uptake and utilization [(5)]. As many as 70% of PCOS women are insulin resistant and 10% have diabetes mellitus (DM) [(6,7)].

Ghrelin is a peptide hormone consists of 28 amino acids; it is synthesized mainly in stomach [(8)]. Because circulating levels of ghrelin increases during fasting and decreases rapidly after a

meal, it is believed that ghrelin has a role in acute changes in energy balance and satiety [9]. It is also a pleiotropic hormone that can influence different metabolic functions such as inducing positive energy balance, increasing food intake, promoting enlargement of adipocytes and also releasing growth hormone [10], and so, it is a hormone that strictly related to obesity, insulin resistance and most probably to the reproductive function. Recently accumulating data suggest that ghrelin has central and peripheral effects on glucose regulation and insulin level [11].

As PCOS predisposes to obesity and metabolic changes such as insulin resistance, it may be assumed that ghrelin's function is connected with this syndrome [12,13]. In the other hand, adolescent obese polycystic ovarian syndrome (which is characterized by insulin resistance) patients had lower ghrelin level compared with lean subjects and ghrelin was negatively correlated with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [14]. The present study was undertaken to investigate the relation between insulin resistance and ghrelin hormone in a sample of Iraqi women with polycystic ovary syndrome.

Methods

A case control study was carried out from November 2012 till June 2013. A total of 69 women aged between (18-45) years were attending from Al-Imamian Al-Khadhmiyian Medical City and Higher Institute for Infertility and Assisted Reproductive Techniques in Baghdad.

Thirty nine out of 69 women were patients diagnosed by their physicians as polycystic ovary syndrome compared with thirty apparently healthy women who shared as control. Patients and control were with a comparable age.

All disorders that can results in menstrual irregularity and hyperandrogenism, including adrenal or ovarian tumors, thyroid dysfunction, congenital adrenal hyperplasia, hyper-prolactinaemia (caused by pituitary diseases), acromegaly, Cushing syndrome, and other causes of infertility besides PCOS were excluded from the study.

A fasting serum sample was used to determine, glucose, lipid profile including total cholesterol, triglyceride (TG), VLDL-C, and HDL-C [measured by the precipitation of chylomicrons] done using colorimetric enzymatic method using Biomaghreb, Sa, France kit.[15] LDL-C was calculated if TG < 400 mg/dl by the formula of Friedewald *et al.* [16] Body mass index (BMI) was calculated by dividing study subjects weight (Kg) on their height (m^2).

Serum ghrelin concentration was measured using an Enzyme Linked immunosorbant Assay (ELISA) technique; Human ghrelin (ghr) ELISA Kit (DRG Instruments GmbH, Germany). Expected normal concentrations are between (346-719 pg/ml). Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured by using enzyme immunoassay sandwich method with a final fluorescent detection (ELFA) (Biomerieux, Sa, France) with reference ranges (1.5-8.0) mIU/ml and (3.9-12.0) mIU/ml respectively.

Ethical approval and patient permission were obtained from the local ethics committee to conduct this study.

Regarding Insulin resistance (IR), HOMA-IR index (homeostasis model assessment of insulin resistance) [17] of the PCOS patients was calculated from fasting glucose and insulin levels as the following equation: Fasting serum insulin (mU/l) × fasting plasma glucose (mg/dl) /405. While QUICKI -index index (Quantitative Insulin Sensitivity Check) was used for measurement of insulin sensitivity from the following equation: 1 / (log F. Insulin+log FBG) [18].

Statistical analysis

Data were statistically analyzed by SPSS version 16. All data were presented as a mean ± SE. Statistical differences between data of patients and control groups were determined according to student *t*-test. Correlation between the variables was performed by Pearson's correlation coefficient. *P* values were significant if < 0.05.

Results

Sixty nine women aged between (18-45) years were divided into 2 groups: Patient's group: includes 39 with PCOS and control group includes 30 apparently normal healthy women. This study was design to compare between the level of ghrelin and other biochemical parameters in addition to insulin resistance in PCOS patients and healthy women.

Regarding anthropometric parameters (age and BMI), no significance was found between patients and control ages (P = 0.391), while a highly significant differences was found between their BMI (P < 0.001) (Table 1).

The higher percentage (33.33%) was found among overweight PCOS women with BMI (25-29.9 Kg/m^2) compared with (46.67%) healthy normal women at the same BMI interval, while the lowest percentage was found among those with normal BMI (7.69 %) compared with (40.0 %) healthy subjects at the same BMI interval. In contrast, the lowest percentages regarding healthy subjects were found among obese and very obese BMI with 6.67% for both (Table 2).

Table 1. Comparison between patients and control anthropometric parameters

Anthropometric parameter	Patients N = 39	Controls N = 30	P value
Age (years)	30.60 ± 1.40	32.18 ± 1.19	NS
BMI (Kg/m^2)	31.83 ± 0.82	26.21 ± 0.82	< 0.001

BMI= Body mass index

Table 2 Comparison between patients and control BMI intervals

BMI	Patients N = 39		Control N = 30		Total		*P* value
	No.	%	No.	%	No.	%	
Normal (< 25 Kg/m^2)	3	7.69	12	40.00	15	21.74	0.001*
Over weight (25-29.9 Kg/m^2)	13	33.33	14	46.67	27	39.13	
Obese (30-34.9 Kg/m^2)	11	28.21	2	6.67	13	18.84	
Very obese (35-39.9 Kg/m^2)	10	25.64	2	6. 67	12	17.39	
Morbid obesity (> 40 Kg/m^2)	2	5.13	0	0.00	2	2.90	
Total	30	100	30	100	69	100	
Mean BMI (kg/m^2)± SE	31.83±0.82		26.21±0.82		29.38±0.67		<0.001†

Chi-square test, †Independent sample t-test, SE= Standard error, BMI= Body mass index

In table 3, serum total cholesterol and triglyceride concentrations and atherogenic index (AI) in PCOS group were found significantly higher than in healthy controls with P value = 0.011, 0.004, 0.002 respectively. No significant difference was found between patients and control FBG level in this study.

PCOS LH, TES, and insulin hormone levels were significantly higher *vs.* control with P = 0.008, 0.035, and < 0.001 respectively as shown in table 4, while patients ghrelin level and fasting glucose/insulin ratio were found significantly decreased compared with the control with P < 0.001.

PCOS HOMA-IR was significantly higher compared *vs.* healthy control (5.77±0.69 *vs.* 2.20±0.29; P < 0.001), while their QUICKI -index was significantly lower than found in control women with (0.31± 0.00 *vs.* 0.35 ± 0.00 and P < 0.001) as noticed in table 5.

No significant correlations were found between patient's ghrelin and all biochemical parameters except with HDL-C with P = 0.02 (Table 6), while

their insulin hormone was correlated significantly with IR index ($P < 0.0001$).

Table 3. Comparison between biochemical parameters of patients and healthy control subjects

Parameters	Controls N = 30 Mean ± SE	Patients N = 39 Mean ± SE	P value
FBG (mg/dl)	91.73 ± 7.81	94.05 ± 1.94	0.748
Cholesterol (mg/dl)	157.40 ± 4.58	175.97 ± 5.18	0.011
Triglyceride (mg/dl)	75.23 ± 5.11	100.38 ± 6.81	0.004
HDL-C (mg/dl)	56.70 ± 1.98	53.28 ± 2.11	0.254
VLDL-C (mg/dl)	16.78 ± 1.80	27.13 ± 4.63	0.065
LDL-C(mg/dl)	85.96 ± 3.93	98.91 ± 6.56	0.096
AI	1.55 ± 0.10	2.12 ± 0.15	0.002

FBG= Fasting blood glucose, HDL-C=High density lipoprotein, VLDL-C= Very low density lipoprotein, LDL-C=Low density lipoprotein, AI =Atherogenic index.

Table 4. Comparison between patients and healthy control hormones

Parameters	Control Group N = 3 Mean±SE	Patients Group N = 39 Mean±SE	*P* value
LH (mIU/ml)	4.56 ± 0.52	9.35 ± 1.64	0.008
FSH (mIU/ml)	5.22 ± 0.39	4.59 ± 0.36	0.255
TES (ng/ml)	0.30 ± 0.03	0.94 ± 0.29	0.035
Insulin (µU/ml)	9.32 ± 0.38	25.03 ± 3.09	< 0.001
Ghrelin (pg/ml)	489.70 ± 53.41	235.10 ± 17.36	< 0.001
FBG/Finslin	9.93 ± 0.61	5.38 ± 0.45	< 0.001
FIns×FBG	890.21 ± 115.58	2334.90 ± 280.52	< 0.001

LH= Luteinizing hormone, FSH= Follicle-stimulating hormone, TES = Testosterone hormone, FBG/Finslin= Fasting blood glucose/Fasting insulin ratio, FIns×FBG= Fasting insulin× Fasting blood glucose.

Table 5. Insulin resistance indexes (HOMA-IR index) in the patients and control groups

Insulin resistances indexes	Patients		control		Total		P value
	No.	%	No.	%	No.	%	
Resistant (> 3.5)	24	61.54	0	3.33	24	34.78	
No (< 3.5)	15	38.46	30	96.67	45	65.21	< 0.001
Total	39	100	30	100	69	100	
Mean HOMA- index	5.77±0.69		2.20±0.29		4.21±3.83		< 0.001
Mean QUICKI- index	0.31±0.00		0.35±0.00		-------		< 0.001

HOMA-IR index= Homeostasis model assessment, QUICKI-IR index= Quantitative Insulin Sensitivity Check

Discussion

PCOS is the most common endocrine disorder in women of reproductive age [19]. Obesity by itself represents an unfavorable metabolic state. A high percentage of PCOS patients is indeed overweight or obese (20-85%) [20]. Most of PCOS patients in this study were overweighed (33.33%), and (28.21%) were obese, and lesser

were very obese with (25.64%). These results are in agreement with other data comparing women with PCOS and age-matched controls; the women with PCOS demonstrated a lower proportion of BMI<25 kg/m^2 and higher proportion of BMI > 30 kg/m^2 and 40 kg/m^2 [21].

Also, Moran *et al*. 2010 reported that the severity of obesity, and especially of abdominal fat disposition, seems in proportion to the severity of the clinical and endocrinological manifestations [22].

Table 6. Correlation between patient's insulin and ghrelin hormone levels with some biochemical parameters

Parameters	Correlation parameters	Insulin (µU/ml)	Ghrelin (pg/ml)
FBG (mg/dl)	r	-0.085	0.004
	P	0.609	0.981
Cholesterol (mg/dl)	r	-0.044	-0.109
	P	0.792	0.509
Triglyceride (mg/dl)	r	-0.372*	-0.045
	P	0.020	0.786
HDL-C (mg/dl)	r	-0.065	0.371*
	P	0.694	0.020
VLDL-C (mg/dl)	r	-0.227	-0.103
	P	0.165	0.533
LDL-C (mg/dl)	r	0.144	-0.159
	P	0.382	0.334
AI	r	-0.014	-0.130
	P	0.932	0.429
LH (mIU/ml)	r	-0.195	0.166
	P	0.234	0.312
FSH (mIU/ml)	r	-0.053	-0.147
	P	0.750	0.373
TES (ng/ml)	r	-0.207	-0.120
	P	0.212	0.472
Insulin resistance	r	0.983**	-0.012
	P	0.000	0.943

* $P < 0.05$, ** = $P < 0.01$, LH = Luteinizing hormone, FSH = Follicle stimulating hormone, TES: Testosterone hormone, FBG = Fasting blood glucose, HDL-C = High density lipoprotein, VLDL-C = Very low density lipoprotein, LDL-C = low density lipoprotein, AI = Atherogenic index.

In addition to that, PCOS patients with normal BMI are also found to present with adverse metabolic profiles [23] in this study with BMI < 25 kg/m^2. However, not all obese females have PCOS and not all PCOS patients are obese (Escober and Morreate, 2005) [24].

Obesity is one of the clinical characteristics of the PCOS along with oligomenorrhea, hirsutism, and infertility and it results from a chronic imbalance between energy intake and energy expenditure [25].

Although several studies have shown that women with excess body weight are more likely to have fertility problems [26], and many researchers believed that obesity is more prevalent in women suffering from PCOS [27]. Results of present study showed BMI of PCOS were ranging from normal to over obese.

The cause of obesity in the PCOS patients remains unknown; however, it is thought that obesity may play a pathogenetic role in the development of the syndrome in susceptible individuals [28]. In 2001 in Iraq, Azziz *et al* reported that PCOS patients have a higher body weight than their counterparts. They suggested that this result may due to the different nutritional habits in Iraq than other countries [29]. Their findings were similar to Carmina *et al.,* 2003 [30].

PCOS includes metabolic abnormalities like changes in reproductive hormones, glucose metabolism and lipid profile changes [20]. Levels of total cholesterol, LDL-C, VLDL-C, triglyceride and atherogenic index (AI) were significantly increase in PCOS patients sera more than control (table 3), while the HDL-C was significantly decrease. This result was agreed with Moran *et al.,* 2010 whom concluded it may potentially cause cardiovascular disease (CVD) [12].

A high percentage of patients with PCOS have abnormal lipid profiles including increased total cholesterol, triglyceride, and LDL-C, whereas HDL-C levels are decreased. Many retrospective studies found significantly increased risk of hypertension and cardiovascular disease (CVD) in women with irregular cycles and the current estimated risk for CVD is 4-11 fold increased in PCOS [31].

Regarding LH and FSH hormones level in this study, PCOS patients LH level was increased significantly more than controls unlike FSH, which was not significant. In addition to that, LH / FSH ratio of cases study was about (2.1). Their result agreed with Asmathulla *et al*., 2013 and Ketel *et al.*, 2009 whom reported that androgen and LH concentrations were increased in both normal weight and obese women suffering from PCOS, while FSH was slightly lower in the normal weight women with PCOS as compared to the normal weight controls. In their study, LH/FSH ratio of 33 patients (56.89%) was above 2 and in 25 (43.1%) cases the ratio was less than 2 [31,32].

Fasting BG, F. insulin, HOMA-IR index and Quicki-IR index were used to evaluate the status of insulin resistance in the two study groups.

Women with PCOS have a high incidence of insulin resistance, a HOMA–IR value > 3.5 probably reflects severe IR, [33], and the QUICKI index is useful for measuring insulin sensitivity, which is the inverse of insulin resistance [34]. In the present study, the incidence was 61.54% (by HOMA-IR method) (Table 5). Although there was no significant difference in fasting glucose levels between control and PCOS women {the entire PCOS patients participant in the present study had normal glucose levels of mean $\pm$SE (94.05$\pm$1.94)}, significantly higher fasting insulin levels were found in the PCOS women. This indicates that the normal fasting glucose value is due to the effect of compensatory hyperinsulinaemia, *i.e*. increased insulin secretion to overcome the insulin resistance [35]. This can be caused by a post –binding defect in signal transduction in women with PCOS. The defect results in a selective insulin activity in the target organs, which causes impaired cellular glucose uptake [36].

Regarding ghrelin, PCOS patients have lower level compared to controls in this study. Mitkov *et al.,* 2008 and Shiva et al*.,* 2012 have showed similar results [37,38]. In studies conducted by Kamal *et al.* 2010, and Glintborg *et al.,* 2006, serum ghrelin concentration was found lower in the PCOS group than in healthy controls [39,40]. Despite these results, Wasko *et al.,* 2004 have reported elevated levels of plasma ghrelin in PCOS patients compared to healthy controls [41]. This discrepancy of results may be explained by confounding factors, such as body weight, fat mass, age, hormonal status, and severity of disease. The reduced fasting ghrelin levels and the relatively smaller increase in ghrelin after weight loss suggest a greater suppression of appetite in obesity and a reduced increase in appetite in weight loss. Moreover, it have been now demonstrated that subjects with PCOS are significantly hungrier and less acutely satiated after a test meal. These observations suggest that subjects with PCOS have impaired defenses against overeating and may not have as strong a drive for meal termination as non-PCOS subjects, the reason for these observed differences in

ghrelin between subjects with and without PCOS are unclear. Similar findings to our study, Schofl *et al.* 2002 showed that ghrelin level did not correlate with BMI [42]. On the other hand, in 2011, Daghestani *et al.* showed a significant inverse relationship between ghrelin and BMI in both PCOS and healthy subjects [43].

From the no significance relation between PCOS ghrelin and most of their biochemical parameters, it can suggest that these biochemical characteristic of PCOS are not affected by ghrelin, and this finding is similar to Pagotto *et al*., 2002 results. They have reported the same findings [44]. Caminos *et al* 2003 [45] have concluded that the ghrelin receptor is found not only in the CNS but also in the ovarian tissues, suggesting a possible reproductive function. Moreover, the capability of ghrelin to alter stimulated testosterone secretion in -*vitro* has been documented [46]. In previous studies there were reports of no significant association [48] and an inverse association have found between serum levels of ghrelin and testosterone [43].

Also, the present results is similar to previous studies that found decreased ghrelin levels in insulin resistant PCOS patients compared with healthy controls matched controls [40,41].

Despite the high circulating level of insulin in PCOS of this study, there was not a significant correlation between their FBG and fasting ghrelin concentrations. This may be due to unmatched BMI among PCOS group. Although many observations support interactions between ghrelin, insulin, and carbohydrate metabolism in PCOS patients, the exact nature of these interactions is not yet clarified, and conflicting results have been reported. *In -vivo* infusion of ghrelin acutely increases serum glucose levels and decreases insulin secretion [42]. Because ghrelin is expressed in pancreatic islet-cells, it may exert direct inhibitory actions on insulin release [44]. Other *in- vivo* and *in- vitro* data suggests a stimulatory action of ghrelin on insulin release [45].

In comparison to matched controls, PCOS women had greater serum insulin levels, confirming previous reports. Low ghrelin levels were associated with increased insulin levels and increased diabetes risk, thus suggesting ghrelin to be an independent risk factor of type-2 diabetes [46].

Orio *et al.* found higher fasting insulin levels in PCOS patients compared with controls but similar ghrelin levels [36], thus supporting a minor importance of insulin for ghrelin secretion. Also Orio *et al.* and Villa 2011 demonstrated significantly inverse correlations between ghrelin and BMI in PCOS, whereas correlations between insulin and ghrelin were non-significant [36,47].

In conclusion, ghrelin hormone in PCOS patients was significantly lower than healthy controls, so it may be used as a new additional marker in PCOS diagnosis. Also, hyperinsulinaemia and hyperleptinemia are associated features in PCOS, and BMI of PCOS patients was ranging from normal to morbid obesity.

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Author Contribution

Study conception and design by Dr. Alaa Ghani and Dr. Rayah Baban, acquisition of data by Dr. Thaer Wali and analysis and Interpretation of data by Dr. Rayah Baban.

Conflict of Interest

The authors declare no conflict of interest.

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