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Research Article

ADIPONECTIN TO LEPTIN RATIO AS A MARKER OF INSULIN RESISTANCE IN WOMEN WITH *POLYCYSTIC OVARY SYNDROME* (PCOS) IN RELATION TO BMI

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ABSTRACT

Polycystic ovarian syndrome is commonly known endocrine disorder in women of reproductive age, PCOS has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression). Insulin resistance (IR) is a defining characteristic of polycystic ovary syndrome,both lean and obese patients with PCOS have been found to be at risk for insulin resistance and type 2 diabetes mellitus. Meanwhile, leptin and adiponectin exert powerful effects on blood glucose homeostasis.

This study was aimed to evaluate the adiponectin to leptin ratio (ALR) as a marker of insulin resistance in women with polycystic ovary syndrome (PCOS) by examination the correlation of ALR with the glycemic indices and other studied parameters in patients with PCOS in comparison to their control groups with respect to BMI.

Fasting blood specimens from forty two women with polycystic ovary syndrome (PCOS) (22 non-obese with BMI <30 and 20 obese with BMI≥30)whom are attending Kamal Al-Samarraee for Infertility and in vitro Fertilization Hospital in Baghdad/Iraq, besides forty seven apparently healthy women (27 non-obese with BMI <30 and 20 obese with BMI≥30).For assessment of serum levels of glucose (FSG) , insulin (FSI), adiponectin and leptin by ELISA kits .

QUIKI and HOMA-IR were significantly different in PCOS groups as compared to their control, the mean serum adiponectin levels were significantly decreased in obese PCOS women (20.14 ± 2.61ng/ml) as compared with the control (33.77 ± 4.98ng/ml), furthermore, it was significantly lowered in non-obese PCOS in comparison to the control (31.91 ± 4.86ng/ml ,42.96 ± 3.96ng/ml respectively). Whereas, serum leptin levels were not significantly changed in PCOS groups as compared with the control.

Thus, ALR ratio could be considered as a good marker for early detection of IR in obese apparently healthy subjects and in non-obese PCOS , and to be more indicative for insulin sensitivity than considering W/H ratio which is related to adiponectin & leptin secretion.

Keywords: PCOS, ALR, Adiponectin, Lepin.

INTRODUCTION

Polycystic ovarian syndrome is a common endocrine disorder affects women of reproductive age [(1)].Clinical features of PCOS include those related to reproductive manifestations such as reduced frequency of ovulation, irregular menstrual cycles, reduced fertility, polycystic ovaries on ultrasound, and high concentrations of male hormones such as testosterone, which can lead to excess facial or body hair growth and acne.

PCOS has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression) that could even worsen quality of life. [(2)] .It was firstly diagnosed in 1935 while Stein and Leventhal observed a group of women who suffered from sterility,

oligomenorrhoea, or amenorrhea, hirsutism, and polycystic ovaries[3].

Insulin resistance (IR) is a defining characteristic of polycystic ovary syndrome, occurring in 50-70% of the PCOS population [4], it is an impaired metabolic response, which occurs when cells cease to respond to ordinary levels of insulin [5].The prevalence of insulin resistance (IR) in PCOS patients have ranged from 44 to 70% [6]. This wide range of prevalence may be due to several factors:

1. The heterogeneity of the diagnostic criteria for PCOS employed in these studies [7],
2. The genetic background among the assessed population [8],
3. The differences regarding the methods used for defining IR [7].

Both lean and obese patients with PCOS have been found to be at risk for insulin resistance and type 2 diabetes mellitus [9]. Non-obese women exhibit lower insulinemia and IR.

The importance of IR in the development of PCOS, both obese and non-obese patients have been related to specific mechanisms causing ovarian dysfunction , which some of them are independent of IR, reflecting the complexity of this syndrome.[10]

Plasma levels of adiponectin (an adipokine) are strongly correlated with insulin sensitivity evaluated by glucose disposal rate[11] suggesting that adiponectin has an important role in insulin actions and hypoadiponectinemia may result in insulin resistance and diabetes mellitus. The association between PCOS and adiponectin level revealed that patient have lower adiponectin compared to controls, and females with a family history of PCOS were significantly more likely to have to lower adiponectin compared to those who did not have family history of PCOS [12].

Meanwhile,leptin (another adipokine) exerts a powerful effect on blood glucose homeostasis[13]. Its main role appears to control body weight through the regulation of appetite and thermogenesis [14]. Most studies, however, did not find any significant differences in serum leptin levels in women with PCOS when compared with age- and weight-matched controls.[15] Other studies find an increased serum leptin concentrations in women with PCOS in comparison to weight-matched controls.[16]

Levels of the serum adiponectin are inversely correlated with body fat percentage in adults(16),and were negatively correlated with WHR, independent of gender and overall adiposity[17]. According to Poretsky et al. (1999) insulin, leptin, body weight, ovarian steroidogenesis and ovulation show complex interrelations [18]. And leptin concentration were directly associated with BMI and waist circumference[19].

MATERIALS & METHODS

Patient selection

This study was carried out at Kamal Al-Samarraee for Infertility and in vitro Fertilization Hospital in Baghdad, for the period from December/ 2014 to May/ 2015. This study included women attending the hospital whom were diagnosed to have PCOS. In addition to two groups of apparently healthy fertile control women (age and BMI matching the patients groups):

-Group1 (C1): 27 obese women (aged 25-45 years, have BMI30 < 30 kg/m2).

-Group2 (C2): 20 non-obese women (aged 25-45 years, have BMI ≥ 30 kg/m2).

Subjects' selection and enrollment in this study was performed under supervision of specialized physicians after the exclusion of related disorders by considering the following criteria:Women should have no prominent chronic liver, kidney, heart diseases or other endocrine disorders ,premenopausal women and their age must be between (25-45) years ,no use of medication nor oral contraceptive, women should be non-pregnant or breast-feeding ,have regular menstrual cycle (26 to 30 days) and Specimens should be collected during the follicular phase (the first 14 days after beginning of menstrual cycle) [20].

Patient was diagnosed by having any two of the following three features according to Rotterdam criteria [21] for diagnosis of PCOS:

1) oligo- or anovulation,

2) Clinical and/or biochemical signs of hyperandrogenism

3) And polycystic ovaries. (Ultrasound imaging)

Those selected patients were allocated into two groups:

-Group1 (D1): 22 obese women (aged 25-45 years, have BMI<30 kg/m2)

-Group2 (D2): 20 non-obese women (aged 25-45 years, have BMI ≥30 kg/m2)

The baseline characteristics for the selected female subjects to be included in the study are illustrated in (table -1).

Biochemical Analysis

Serum glucose levels was determined according to Barham and Trindoer method[22], fasting serum insulin was assessed by using the solid phase enzyme linked assay (ELISA) [23]. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)was calculated as a marker of insulin resistance [24] and QUIKI as a marker for insulin sensitivity [25]. Serum adiponectin concentration[26] and serum leptin concentration[27] were measured by using the demeditec ELISA (Demeditic Diagnostics, Germany)

The Statistical Analysis System- SAS (2012) was used to express the different factors in study parameters. Least significant difference –LSD test was used to significant comparison between means, the results were expressed as mean ± standard error of mean.Pearson's correlation coefficient (r) was used to test for statistically significant correlation between studied parameters.

RESULTS

Fasting serum glucose values were not significantly different between different groups, while, fating serum insulin measurements were significantlyelevated in PCOS groups.

Furthermore, serum adiponectin values and serum leptin values were different obviously between studied groups, (Table-2).

Pearson 's correlation coefficient between ALR with other studied parameters in PCOS groups and their BMI-matched controls was determined to examine any significant correlation among these markers (Table-3).

There was a significant negative correlation between FSG and ALR in obese control women. While, FSI and HOMA-IR were correlated significantly with ALR in obese control women and non-obese PCOS women.

HOMA-IR and QUIKI values were correlated significantly with FSI in all studied groups as shown in (table-4), (table-5) respectively.

Table 1: Baseline Characteristics of Subject involved in the Study

Groups → Parameters	Control women (C) (Healthy)	PCOS women (Patients)	LSD value	P-value
Number	47	42	_____	_____
Age (yrs.)	33.11 ± 0.82	28.83 ± 0.76	2.233 *	0.0003
BMI(kg/m^2)	29.13 ± 0.80	30.80 ± 0.87	2.352(NS)	0.164
W:H ratio	0.836 ± 0.007	0.862 ± 0.005	0.0185 **	0.0056
FSG (mg/dl)	87.50 ± 1.64	89.56 ± 1.73	4.740(NS)	0.388
Fasting Insulin (µIU/ml)	16.47 ± 1.89	33.46 ± 4.11	8.695 **	0.0002
QUIKI	0.334 ± 0.006	0.301 ± 0.005	0.0162 **	0.0001
HOMA-IR	3.65 ± 0.42	7.06 ± 0.86	1.850 **	0.0004
Adiponectin (ng/ml)	39.05 ± 3.14	26.31 ± 2.95	8.637 **	0.0043
Leptin (ng/ml)	44.84 ± 3.42	41.47 ± 3.52	9.786(NS)	0.494
ALR	1.63 ± 0.33	1.32 ± 0.32	0.929(NS)	0.503

-Data are expressed as Mean±SD. BMI: body mass index. yrs:years, cm: centimeter, W:H ratio: waist to hip circumference ratio, DM: diabetes mellitus,FSG:fasting serum glucose, QUIKI: Quantitative Insulin Sensitivity Check Index, HOMA-IR:Homeostatic Model Assessment of Insulin Resistance,LH:luteinizinghormone,FSH:follicle stimulating hormone, ALR:adiponectin to leptin ratio.

** indicate that means in the same row are significantly differed (P<0.05).

Table 2: Measured Parameters among Studied Groups.

Groups → / Parameters ↓	Control women with BMI <30 kg/m2 (C1) (n=27)	Control women with BMI ≥30 kg/m2 (C2) (n=20)	PCOS women with BMI <30 kg/m2 (D1) (n=22)	PCOS women with BMI ≥30 kg/m2 (D2) (n=20)	LSD value	P value
FSG(mg/dl)	85.02 ± 1.97	90.84 ± 2.65	88.33 ± 1.53	90.92 ± 3.24	6.681 NS	0.223
Fasting Insulin (MIU/ml)	13.42 ± 1.69	20.58 ± 3.67	27.91 ± 4.71	39.57 ± 6.78	12.174 **	0.0004
HOMA-IR	2.87 ± 0.36	4.70 ± 0.82	5.46 ± 0.81	8.82 ± 1.49	2.536 **	0.0001
QUIKI	0.341 ± 0.02	0.324 ± 0.01	0.305 ± 0.01	0.296 ± 0.01	0.023 **	0.0004
Adiponectin (ng/ml)	42.96 ± 3.96	33.77 ± 4.98	31.91 ± 4.86	20.14 ± 2.61	12.014 **	0.0030
Leptin(ng/ml)	39.54 ± 4.61	52.01 ± 4.77	34.39 ± 4.84	49.26 ± 4.64	13.457 *	0.0401
ALR	2.27 ± 0.54	0.766 ± 0.11	1.62 ± 0.36	0.986 ± 0.55	1.289 *	0.056

Table 3: Correlations of ALR with the studied parameters in different groups.

Groups / Parameter	Control women with BMI <30 kg/m2 (C1) (n=27)		Control women with BMI ≥30 kg/m2 (C2) (n=20)		PCOS women with BMI <30 kg/m2 (D1) (n=22)		PCOS women with BMI ≥30 kg/m2 (D2) (n=20)	
	r	P	r	P	r	p	r	p
W/H Ratio	0.03477	0.8633	0.27025	0.2492	-0.04703	0.8354	-0.39085	0.0884
FSG	0.14883	0.4588	-0.42555	0.0614*	-0.36642	0.0935	0.10193	0.6689
FSI	-0.07663	0.7040	-0.46832	0.0373*	-0.41747	0.0532*	-0.33738	0.1458
QUICKI	-0.01517	0.9401	0.60427	0.0048*	0.47103	0.0269*	0.67641	0.0011**
HOMA-IR	-0.04658	0.8175	-0.48935	0.0285*	-0.42255	0.0501*	-0.33949	0.1431
Adiponectin	0.60180	0.0009**	0.81164	<.0001**	0.69403	0.0003**	0.62324	0.0033*
Leptin	-0.72164	<.0001**	-0.59060	0.0061*	-0.65162	0.0010**	-0.57540	0.0079*

* Statistically significant ($p<0.05$).

** Highly significant ($p<0.001$).

Table 4: Correlations of HOMA-IR with the studied parameters in different groups

Groups	Control women with BMI <30 kg/m2 (C1) (n=27)		Control women with BMI ≥30 kg/m2 (C2) (n=20)		PCOS women with BMI <30 kg/m2 (D1) (n=22)		PCOS women with BMI ≥30 kg/m2 (D2) (n=20)	
Parameter	**R**	**P**	**r**	**P**	**r**	**p**	**R**	**p**
W/H Ratio	0.13217	0.5111	-0.50267	0.0239*	0.26146	0.2399	0.23137	0.3264
FSG	0.37029	0.0573*	0.36292	0.1158	0.52554	0.0120*	0.13834	0.5608
FSI	0.98636	<.0001**	0.97942	<.0001**	0.80768	<.0001**	0.97352	<.0001**
QUICKI	-0.89099	<.0001**	-0.78669	<.0001**	-0.86388	<.0001**	-0.84924	<.0001**
Adiponectin	0.02977	0.8828	-0.32744	0.1588	-0.32371	0.1417	-0.49306	0.0272*
Leptin	0.22356	0.2623	0.31077	0.1823	0.43392	0.0436*	0.56984	0.0087*
ALR	-0.04658	0.8175	-0.48935	0.0285*	-0.42255	0.0501*	-0.33949	0.1431

* Statistically significant (p<0.05).
** Highly significant (p<0.001).

Table-5: Correlations of QUIKI with the studied parameters in different groups.

Groups	Control women with BMI <30 kg/m2 (C1) (n=27)		Control women with BMI ≥30 kg/m2 (C2) (n=20)		PCOS women with BMI <30 kg/m2 (D1) (n=22)		PCOS women with BMI ≥30 kg/m2 (D2) (n=20)	
Parameter	**R**	**P**	**r**	**P**	**r**	**p**	**R**	**p**
W/H Ratio	-0.31516	0.1093	-0.31516	0.1093	-0.11622	0.6065	-0.29514	0.2065
FSG	-0.55783	0.0025*	-0.55783	0.0025*	-0.50140	0.0174*	-0.18628	0.4317
FSI	-0.87125	<.0001**	-0.87125	<.0001**	-0.88565	<.0001**	-0.82309	<.0001**
HOMA-IR	-0.89099	<.0001**	-0.89099	<.0001**	-0.86388	<.0001**	-0.84924	<.0001**
Adiponectin	-0.15492	0.4404	-0.15492	0.4404	0.30059	0.1741	0.61248	0.0041*
Leptin	-0.16815	0.4018	-0.16815	0.4018	-0.39692	0.0674	-0.67493	0.0011**
ALR	-0.01517	0.9401	-0.48935	0.0285*	0.47103	0.0269*	0.67641	0.0011**

* Statistically significant (p<0.05).
** Highly significant (p<0.001).

DISCSSION

PCOS patients fasting serum insulin levels expressed significant higher levels than their BMI-matched controls, although all the studied groups were normoglycemic. Such variation in serum insulin level is reflected by variation in HOMA-IR and QUIKI values as markers for insulin resistance and sensitivity , respectively .Such inconsistency in these values could indicate early stages of insulin resistance in the studied groups (C2,D1 and D2) despite their normal fasting glucose levels .

However, these results could be related to metabolic disorders in PCOS regarding glucose metabolism as a result of insulin resistance as presented by increased HOMA-IR values among the PCOS patients[28].

Serum adiponectin levels were significantly higher in control healthy women than in PCOS women of the same BMI range,The results of the present study agree with studies find that Circulating adiponectin levels decrease with obesity and increase with weight loss [29, 30, 31]. Serum adiponectin levels have also been reported to be reduced in obese humans, particularly those with visceral obesity, and to correlate inversely with insulin resistance[32, 33].

The role of adiponectin in insulin resistance was determined by using knockout mice. These mice had normal plasma insulin levels but its role in lowering the blood glucose level was severely impaired, this clearly pointing to the role of adiponectin in glucose tolerance [34]. Likewise, the absence of serum adiponectin in lipoatrophic mice causes hyperglycemia and hyperinsulinaemia, which can be normalized by adiponectin injections. The ability of adiponectin to ameliorate insulin resistance has been documented in db/db mice[35]. All studies on the role of adiponectin in insulin resistance are suggest that decreased levels of adiponectin cause susceptibility to these disorders.

Serum leptin concentration were decreased in patient groups in compared with their BMI- matched controls,Yildizhan et al. (2011) observed an association between serum leptin levels with IR in young women with PCOS [36].

Considering the ALR correlations, ALR was negatively correlated with FSG and FSI in the obese control group , but not in other groups.Indicating the importance of obesity in IR development, as noticed by the correlation of ALR with both HOMA-IR and QUIKI.

Whereas, ALR was negatively correlated with FSI in non-obese PCOS group indicating involvement of other factors besides obesity in PCOS. On the other hand HOMA-IR was significantly correlated with FSG in non-obese groups (C1 & D1) of both control & PCOS groups, but with all studied groups FSI.While , QUIKI values were correlated in lean subjects (control &PCOS)with FSG , as well as with FSI.

Thus, ALR ratio could be considered as a good marker for early detection of IR in obese apparently healthy subjects , and to be more indicative for insulin sensitivity than considering W/H ratio which is related to adiponectin & leptin secretion.

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