Document heading   doi:10.1016/S2222−1808(11)60017−0

Evaluation of insulin sensitivity status in polycystic ovarian syndrome

Wilma Delphine Silvia C[1*], Kavya N[2], Sweta Kulkarni[2]

[1]Department of Biochemistry, Sapthagiri Institute of Medical Sciences & Research Centre, Bangalore−560090, India
[2]Department of Biochemistry, Vydehi Institute of Medical Sciences & Research Centre, Bangalore−560066, India

ARTICLE INFO

ABSTRACT

Objective: To identify the risk arising from polycystic ovarian syndrome (PCOS) which would help the clinician to make early interventions. **Methods:** Fasting and postprandial serum glucose and serum insulin levels were estimated in 26 cases of PCOS and 26 healthy women were selected as controls. Calculation of quantitative insulin sensitivity check index (QUICKI) in all the subjects was utilized to analyze its sensitivity and reliability. Also body mass index and waist circumference in all these subjects were measured as obesity plays a key role in the pathogenesis of PCOS. **Results:** Hyperglycemia was observed in 11% of the cases and hyperinsulinemia was a consistent feature in 46% of the patients. The postprandial insulin levels in cases were statistically significant (P=0.006). Sensitivity to insulin as indicated by QUICKI in the postprandial state was less in cases than in controls (P=0.13). The BMI was markedly raised in 15% and moderately raised in about 38% of the cases (P=0.024). Waist circumference was significantly raised in about 61% of the cases (>80 cm) (P<0.001). **Conclusions:** Our study indicates that QUICKI, BMI and waist circumference are simple, quick and may act as early markers in identifying the risks of developing metabolic syndrome. Obesity, being a consistent finding in most cases suggested its key role in the pathogenesis of PCOS.

1. Introduction

Polycystic ovarian syndrome (PCOS) also known as Stein−Leventhal syndrome is a heterogeneous, multifactorial, polygenic condition and an established cause of infertility[1]. PCOS is characterized principally by oligomenorrhea/amenorrhea, clinical or laboratory evidence of hyperandrogenemia and detection of polycystic ovaries by ultrasound and presence of 10 or more cysts of 2−10 mm in diameter in each ovary. Furthermore, it is now recognized that a significant proportion *i.e.*, 80% of women with PCOS have hyperinsulinemia[2].

Insulin resistance in women with PCOS may eventually lead to the development of hyperglycemia and type 2 diabetes mellitus and thus they are at a higher risk of developing metabolic syndrome[3]. In an effort to counter the effect of excess insulin in PCOS, insulin−sensitizing agents are commonly used, although FDA, USA have not yet approved this. In addition, Android obesity occurs in more than 50% of patients[4], which indicates an increased risk of diabetes mellitus, dyslipidemia, gestational diabetes, cardiovascular diseases[5]. This study aimed at identifying this risk which would help the clinician to make early interventions. In this regard, we estimated fasting and postprandial serum glucose and insulin levels in PCOS and calculated quantitative insulin sensitivity (QUICKI), to analyze their sensitivity and reliability[6].

2. Materials and methods

2.1. Participants

This case control study was conducted in the year 2010 at Vydehi Institute of Medical Sciences and Research Centre, Bangalore and 26 healthy female controls aged 18−40 years and 26 age and sex−matched patients who were clinically confirmed cases of polycystic ovarian syndrome were included. An informed consent was taken from the patients for the study. Women suffering from chronic liver, kidney, thyroid, cardiovascular diseases, autoimmune disorders and other causes for hirsutism, hyperandrogenism and amenorrhoea were excluded. This study was approved by

*Corresponding author: Dr. Wilma Delphine Silvia CR, MD., DNB, Professor and Head, Department of Biochemistry, Sapthagiri Institute of Medical Sciences and Research Centre #15, Chikkasandra, Hesaraghatta Main Road, Bangalore 560090, Karnataka, India.
  Tel: 09448169967
  E−mail: widel2008@gmail.com; widel@rediffmail.com

the institution's ethics committee, and informed consent was obtained from every subject.

2.2. Sample collection and method

Under aseptic precaution, 5 mL samples of fasting and postprandial blood samples were collected in plain vacutainers. Clotted blood was centrifuged. The clear serum was separated and used for the measurement of fasting and postprandial blood sugar levels by Glucose Oxidase Method (Beckmen Coulter, USA), serum insulin levels by electrochemiluminescence immunoassay by using insulin kits (Roche diagnostics, Mannheim, USA).

QUICKI[7] was utilized to determine the level of insulin sensitivity as QUICKI=1/[log (Ins) + log (Glu)] where, (Ins) and (Glu) refer to serum insulin and plasma glucose levels respectively.

Body mass index=Weight (kg)/Height (m^2)[8]. Waist circumference (WC) was measured in orthostatic position at the midpoint between the lateral iliac crest and lowest rib[9].

2.3. Statistical analysis

Descriptive statistical analysis was carried out in the present study. Results on continuous measurements were expressed as Mean±SD (Min–Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level. Student t–test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Pearson correlation between variables was computed in cases and controls.

The statistical software namely SPSS 15.0 was used for the analysis of the data and Microsoft word and Excel was used to generate graphs, tables, *etc.*

3. Results

Study included the PCOS cases diagnosed clinically and ultrasonographically with features of PCOS–oligomenorrhea, hyperandrogenemia, presence of cysts as per the Rotterdam criteria for PCOS[10].

The BMI was raised in 53% of the cases with mean±SD of 26.09±3.95 in contrast to 38% of controls where BMI was moderately raised. Thus there was a statistically significant raise in BMI in cases (P=0.024) (Table 1).

Table 1
BMI distribution between cases and controls.

BMI	Cases [n (%)]	Controls [n (%)]
18–25.0	12 (45.2)	16 (61.5)
25.0–30.0	10 (38.5)	10 (38.5)
>30.0	4 (15.4)	0 (0.0)
Total	26 (100.0)	26 (100.0)

Table 2
Comparison of insulin sensitivity variables between controls and cases.

Variables	Cases	Controls
Age in years	25.96±5.61	27.42±4.91
BMI (kg/m^2)	26.09±3.95*	23.77±3.17
WC (inches)	84.69±15.55**	68.65±12.97
FBS (mg/dL)	91.92±12.26	94.62±13.90
PPBS (mg/dL)	144.54±24.88	143.15±18.18
Fasting insulin (mIU/L)	13.56±8.28	11.16±3.83
PP insulin (mIU/L)	68.47±27.49**	49.35±20.16
QUICKI–Fasting	0.36±0.12	0.33±0.02
QUICKI–PP	0.25±0.02	0.26±0.02

*: P<0.05, **: P<0.01.

Table 3
Pearson's correlation between variables studied in cases.

Variables	BMI	WC	FBS	PPBS	Fasting insulin	PP insulin	Fasting QUICKI	PP QUICKI
Insulin								
Age in years	−0.301	−0.096	0.130	−0.015	0.158	0.016	−0.194	−0.033
BMI (kg/m^2)	–	0.495*	0.012	0.273	0.236	0.338	−0.005	−0.349
WC (inches)	–	–	0.013	0.302	0.390*	0.303	−0.072	−0.297
FBS (mg/dL)	–	–	–	0.444*	−0.299	−0.138	0.258	−0.150
PPBS (mg/dL)	–	–	–	–	−0.132	0.112	0.253	−0.384
Fasting insulin (mIU/L)	–	–	–	–	–	0.387	−0.618*	−0.306
PP insulin (mIU/L)	–	–	–	–	–	–	0.152	−0.842**
QUICKI–Fasting	–	–	–	–	–	–	–	−0.095
QUICKI–PP	–	–	–	–	–	–	–	–

PP: post prandial; 0.1–0.3: small correlation; 0.3–0.5: moderate correlation; 0.5–0.7: large correlation; 0.7–0.9: very large correlation; *: P<0.05, **: P<0.01.

Statistically significant raise in waist circumference was found in about 61% of the cases in comparison to controls 19% (*P*<0.001). Waist circumference also correlated with fasting serum insulin levels (Table 2 & 3).

About 11% of cases and 19% of controls were found to be hyperglycemic with a marginal rise in fasting blood sugar levels in cases (91.92±12.26) and post prandial sugar levels (144.54±24.88) (Table 2).

Inspite of the limitation in this study, we observed that hyperinsulinemia was a consistent feature in most of the patients. It was observed that about 19% of the cases had abnormal fasting insulin levels while 46% had abnormal postprandial insulin levels. However, controls had neither fasting nor postprandial hyperinsulinemia. Fasting insulin levels were in the range of 13.56±8.28 while postprandial insulin levels varied as 68.47±27.49 in cases and a highly statistically significant *P* value of 0.006 was obtained (Table 2).

Sensitivity to insulin as indicated by fasting QUICKI was higher in cases (0.36±0.12) than in controls (0.33±0.02) (limitation). However, the postprandial QUICKI was low in cases (0.25±0.02) as compared with controls (0.26±0.02) (Table 2).

The Pearson's correlation was studied for each parameter in cases and it was observed that, there was a significant correlation between BMI and waist circumference and a moderate correlation between waist circumference and fasting serum insulin levels in cases (Table 3).

There was a significant negative correlation between Fasting Blood Sugar and Fasting Insulin levels; and Postprandial Blood Sugar and Postprandial Insulin levels, *i.e.* as the Fasting Blood Sugar increased, Fasting Insulin levels increased, QUICKI decreased indicating low sensitivity to insulin and *vice versa*.

4. Discussion

PCOS is not only a gynecological condition affecting women of reproductive age but also a comprehensive syndrome with a variety of associated metabolic disorders such as insulin resistance, dyslipidaemia[11].The mechanisms leading to the development of PCOS are not yet completely understood. However, it is observed that insulin resistance and hyperinsulinaemia may play an important role in the pathophysiology of PCOS[12] while insulin resistance is associated with obesity[13].

Obesity, particularly central obesity, is a common PCOS feature that worsens its phenotype. Compared with weight–matched healthy women, those with PCOS have a similar amount of total and abdominal fat, but a higher proportion of periomental fat. Additionally, excess periomental fat is associated with an increase in low–grade chronic inflammation and insulin resistance and with metabolic dysfunction in PCOS[14,15]. Increased periomental fat may also be present in non–obese PCOS women, likely contributing to the development of glucose and lipid metabolism disorders.

It is observed during this study that obesity is a consistent finding in most patients. This suggests its key role in the pathogenesis of PCOS, *i.e.* hyperinsulinemia by over activation of hypothalamo–pituitary axis and decreased sensitivity of receptors to insulin.

Obesity–associated defect in insulin sensitivity is the result of both pre– and postreceptor abnormalities[15]. Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes. In obese individuals, adipose tissue releases increased non–esterified fatty acids, glycerol, hormones, pro–inflammatory cytokines and other factors that are involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of pancreatic islet β–cells, there occurs a failure to maintain euglycemic state.

Insulin resistance is a term, which has a broad clinical spectrum and heterogeneities in the manifestations. Degree of insulin resistance can also vary among different clinical states. The concept of insulin resistance is easy to understand but quantitative assessment of insulin sensitivity, which is the reverse of resistance, and the ability to determine exactly who is insulin resistant is more difficult in a clinical setting. However, this assessment of insulin resistance or insulin sensitivity is of great importance in the study of epidemiology and pathophysiology of major public health problems and in the following clinical course of patients on various therapeutic regimens. Insulin sensitivity can be influenced by age, ethnicity, *etc* and obesity is considered as an important independent cause of insulin resistance.

Studies have suggested that all women with PCOS should be considered as insulin resistant[17,18]. But this recommendation does not take into consideration the large differences in insulin sensitivity among women with PCOS. In the present study low QUICKI value was found in the cases of PCOS. Several studies have suggested that a single screening test for PCOS related insulin resistance should be individualized for different racial or ethnic populations[18].

The cause of insulin resistance in PCOS is not fully explained. It is suggested that the post–receptor defect in insulin signaling can be caused by a plasma derived factor, which could activate serine kinase of insulin receptor substrate and in that way inhibit insulin action[19]. Insulin resistance is an independent risk factor for cardiovascular disease and a prevalent metabolic disturbance among women with PCOS.

Obesity as an independent factor for insulin resistance can influence the phenotype of the syndrome and can worsen the endocrine and metabolic parameter. Central adiposity, a marker of insulin resistance and an accurate anthropometric method to estimate android adiposity, may represent a key clinical tool for insulin resistance screening in subpopulations at higher metabolic and cardiovascular risk, such as women with PCOS. Abdominal fat could deliver excess lipid from metabolically labile abdominal adipocytes to muscle, where lipid overabundance impairs muscle insulin action[22].

Though not approved by FDA, currently insulin sensitizing agents like Metformin have been widely used to treat cases of PCOS with primary infertility irrespective of the glycemic

status of the patient. It is observed that Metformin increases ovulation induction from several studies, thus treating primary infertility[21]. The use of Metformin (Glycomet) in cases was an intervention in the study as the true glycemic status of the patients could not be assessed and only a drug –altered glycemic and insulin status of the patient was studied. This was a limitation in our study.

The treatment of PCOS is a complex therapeutic exercise as the pathophysiological events follow various paths. Through this study, we attempted to evaluate insulin resistance and the more recently emerging risk of metabolic syndrome in PCOS.

Insulin sensitizing agents reduce the need for higher insulin production and thereby reduce serum insulin levels. These medications are therefore needed when tissue sensitivity to insulin is low and thus serum insulin levels are elevated. The clinical relevance of this study relates to the more accurate selection of insulin–sensitizing agents in PCOS.

These medications could be avoided in normoglycemic subjects with low insulin levels as these have their own profile of side effects. Life style modification by mere control of obesity would treat the underlying hyperinsulinemia if it is minimal, as indicated by the fasting serum insulin and QUICKI levels.

Estimation of serum insulin levels and QUICKI as a sensitive index can thus provide a valuable guide, whether or not the patient is to be started on insulin senitising agents. If started, keeping in mind to select the best insulin sensitizing agent with the short term ill effects.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynaecol* 1935; **29**: 181–197.

[2] Conway GS. Hyperinsulinaemia and polycystic ovary syndrome. *Hum Fertil* 2000; **3**: 93–95.

[3] Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome; a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999; **84**: 165–169.

[4] Zacur HA. Polycystic ovarian syndrome, hyperandrogenism, insulin resistance. *Obstet Gynaecol Clin North Am* 2001; **28**: 21–23.

[5] Giallauria F, Orio F, Palomba S, Lombardi G, Colao A, Vigorito C. Cardiovascular risk in women with polycystic ovary syndrome. *J Cardiovasc Med (Hagerstown)* 2008; **9**(10): 987–992.

[6] Yeni–Komshian H, Carantoni M, Abbasi F, Reaven GM. Relationship between several surrogate estimates of insulin resistance and quantification of insulin–mediated glucose disposal in 490 healthy nondiabetic volunteers. *Diabetes Care* 2000; **23**: 171–175.

[7] Katz A, Nambi SS, Mather K, Baron AD, Follman DA, Sullivan G. Quantitative Insulin Check Index a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000; **85**; 2402–2410.

[8] Bhattacharya SM. Mathematical indices of insulin resistance and body mass index in polycystic ovarian syndrome. *J Obstet Gynecol India* 2005; **55**: 159–162.

[9] Roopakala MS, Suresh A, Ashtalakshmi, Srinath, Ashok, Giridhar, et al. Anthropometric measurements as predictors of intraabdominal fat thickness. *Indian J Physiol Pharmacol* 2009; **53**(3): 259–264.

[10] Carmina E. Diagnosis of polycystic ovary syndrome: from NIH criteria to ESHRE–ASRM guidelines. *Minerva Gynecol* 2004; **56**(1): 1–6.

[11] Wild S, Pierpoint T, Mc Keigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long–term follow up: a restrospective cohort study. *Clin Endo Crinol (oxf)* 2000; **52**: 595–600.

[12] unaif A. Insulin resistance and polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Res* 1997; **18**: 774–800.

[13] Diamanti–Kandarakis E, Papaxastiline AG. Molecular mechanisms of insulin resistance in polysystic ovary syndrome. *Trends Mol Med* 2006; **12**: 324–334.

[14] Cascella T, Palomba S, Sio ID, Manguso F, Giallauria F, Simone BD, et al. Visceral fat is associated with cardiovascular risk in women with polycystic ovarian syndrome. *Hum Reprod* 2007; **16**: 1–7.

[15] Wiwanitkit V. Hyperglycemia in poor controlled diabetes from crude tamarind herbal pill: a case study. *Asian Pac J Trop Biomed* 2011; **1**(1): 79–80.

[16] Kahn SE, Prigeon RL, Schwartz RS, Fujimoto WY, Knopp RH, Brunzell JD, et al. Obesity, body fat distribution, insulin sensitivity and islet β–cell function as explanations for metabolic diversity. *J Nutr* 2001; **131**: 354–360.

[17] Nestler JE, Powers LP, Matt DW, Matt DW, Steingold KA, Plymate SR, et al. A direct effect of hyperinsulinemia on serum sex hormone binding globulin levels in obese women with PCOS. *J Clin Endocrinol Metab* 1991: **72**: 83–89.

[18] Nestler JE, Stovall D, Akhter N, Iuorno MJ, Jakubowicz DJ. Strategies for the use of insulin–sensitising drugs to treat infertility in women with polycystic ovarian syndrome. *Fertil Steril* 2002; **77**: 209–215.

[19] Kauffman RP, Baker VM, Dimarino P, Gimpel T, Castracane VD. Polycystic ovarian syndrome and insulin resistance in white and Mexican American women: a comparison of two distinct populations. *Am J Obstet Gynecol* 2002; **187**: 1362–1369.

[20] Li M, Youngren JF, Duanif A, Goldfine ID, Maddux BA, Zhang BB, et al. Decreased insulin receptor (IR) autophosphorylation in fibroblasts from patients with PCOS: effects of serine kinase inhibitors and IR activators. *J Clin Endocrinol Metab* 2002; **87**: 4088–4093.

[21] Gan SK, Adamandia D, Kriketos, Bronwyn A, Ellis, Campbell H, et al. Changes in aerobic capacity and visceral fat but not myocyte lipid levels predict increased insulin action after exercise in overweight and obese men. *Diabetes Care*; 2003; **26**: 1706–1713.

[22] Turner MJ, Walsh J, Byrne KM, Murphy C, Langan H, Farah N. Outcome of clinical pregnancies after ovulation induction using metformin. *J Obstet Gynaecol* 2006; **26**(3): 233–235.