ORIGINAL ARTICLE

Serum Insulin Levels, Insulin Resistance and Type 2 Diabetes in Patients of Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous disorder presenting with major clinical features of menstrual irregularities, sub-fertility, hyperandrogenism, and hirsutism. It is considered as the most common endocrinopathy, affecting 4-12% of women of reproductive age.Polycysticovarycontains 12 or more follicles of 2-9 mmdiameter and/or comprising of volume more than (10cm^3). Polycystic ovarian syndrome is usually associated with metabolic disturbances called metabolic syndrome. Exploring pathophysiology of polycystic ovarian syndrome suggests insulin resistance as a key feature leading to type 2 diabetes mellitus.

Aim: To determine and compare serum insulin levels, blood glucose level and HOMA-IR in obese and non-obese patients with polycystic ovaries.

Methodology: In this comparative study, eighty eight females with polycystic ovaries within the age limit of 18-38 were divided into two equal groups, obese and non-obese females.Serum insulin was determined by enzyme linked immunosorbent assay and fasting blood group was determined by enzymatic calorimetric method. Homeostasis model assessment of insulin resistance was measured by using serum fasting glucose and insulin levels. These parameters were compared by appropriate statistical techniques using SPSS 20.0.

Results: Obese women with polycystic ovarian syndrome showed significantly higher fasting levels of serum insulin and insulin resistance as compared tonon-obese women.

Conclusions: Increased insulin resistance in obese women with polycystic ovarian syndrome causes development of type 2 diabetes mellitus in these patients.

Keywords: Polycystic ovarian syndrome, insulin resistance, metabolic syndrome, type 2 diabetes mellitus.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) has a prevalence of 4-12%, revealing it as the most common endocrine disorder of reproductive age women[1, 2]. Polycystic ovary is labeled if 12 or more follicles of 2-9 mm diameter are present in each ovary and/or if ovarian dimensions are of more than (10 cm^3)[3].

Many patients with PCOS have visceral obesity, hyperinsulinaemia and insulin resistance (IR) which are features of metabolic syndrome (MS)[4]. Insights into pathophysiology of PCOS show insulin resistance in around 50% to 80% of overweight women having severe PCOS. As body tissues show resistance to the effects of insulin, excess insulin is produced by the body to have its necessary effects on metabolism of lipids, synthesis of proteins and changes in the rate of androgen production.

In women with PCOS, there is a steady secretion of gonadotropin and sex steroids resulting in anovulation[5]. The frequency of PCOS in infertile patients of two infertility centers of Karachi, was comparable to the rates mentioned from infertility centers in Britain and United States i.e. 20-25%[6].

Polycystic ovarian syndrome patients have twice the risk of developing metabolic syndrome (MS) compared to women from the general population [7].Obesity and IR can lead to features of MS in PCOS women[8]. Obesity is seen in 50% women with PCOS and increased insulin secretion in response to insulin resistance is also shared by the same percentage of patients[9].

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Women with PCOS in Indian Sub-continent have significantly higher levels of fasting insulin and lower rates of insulin sensitivity than Caucasian controls [10]. Metabolic syndrome is found in 46.2% females with PCOS in a study conducted at Kolkata, India[11].

Longstanding IR in these patients is frequently manifested as glucose intolerance, which is an emerging risk factor for T2DM. When hyperglycemia emerges to diabetic level as a result of glucose intolerance, this constitutes an independent risk factor for coronary vascular disease[12].

The mechanism by which obesity, especially visceral fat depots lead to IR is by increasing free fatty acids (FFA) and lactate which are shown to disturb secretion, metabolism and peripheral action of insulin.

Hyperandrogenemia and IR are related to each other and frequently co-exist in PCOS women and predispose to dyslipidemia which is more pronounced in overt diabetes. Hyperandrogenemia contributes to the characteristic body fat distribution linked with IR and MS[13].Hyperinsulinemia secondary to IR in turn inhibits synthesis and stimulates catabolism of DHEA-S, reducing its level and thereby increasing free androgens concentration in blood. The co-existence of PCOS and MS leads to more severe hyperandrogenemia[14].

Paradoxically in PCOS, insulin resistance represents in a way that its stimulation of androgen production continues but effect on glucose metabolism becomes disturbed. Some of the patients with PCOS have insulin resistance and resultant hyperinsulinemia by excessive stimulation of beta cells to such an extent that they burn out resulting in pancreatic insufficiency and frank diabetes mellitus[15].

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MATERIALS AND METHODS

This comparative study was conducted in Department of Physiology, PGMI, Lahorein cooperation with the Lahore General hospital, Lahore. It was approved by the Advanced Science and Research board of the University of Health Sciences (UHS), Lahore.

The research was completed in almost one year (2013). Eighty eight obese and non-obese females with polycystic ovarian syndrome (freshly diagnosed) between 18-38 years of age were selected from the patients visiting Obstetrics and Gynecology outpatient department (OPD), Lahore General Hospital, Lahore. The study population was divided into two groups, Group-1 comprising of 44 obese subjects with PCOS& group 2 including 44 non-obese subjects with PCOS. Patientson any medication, oral contraceptive pills or lipid lowering agents or having other endocrine diseases e.g., adrenal, thyroid, pituitary glandwere excluded. Patients with chronic illness and pregnancy were also excluded from the study.

After obtaining written informed consent from each participant, general and systemic examinations were conducted to rule out any underlying disease. Blood pressure was estimated by using sphygmomanometer. Body mass index was calculated with the help of formula; BMI=body weight (Kg)/ height (m^2).

After aseptic measures, five milliliters of venous blood of the subjects was drawn in a serum vial. The blood taken in serum vials was centrifuged immediately at a speed of 5000 revolutions per minute for ten minutes. The serum samples were secured in properly labeled eppendorf tubes (1.5ml), aliquoted and pending further analysis immediately stored at -20ºC. Blood sample analysis for blood sugar level (BSL) was done on the same day. Insulin was measured quantitatively by using ELISA technique by direct immunoenzymatic colorimetric method using kit named Nova TecImmunodiagnostica GmbH Technologies & Waldpark Waldstr Dietzenbach, Germany. HOMA-IR was calculated by using values of fasting blood glucose and serum insulin levels with the help of following formula:
HOMA-IR = fasting insulin (µIU/ml) × fasting blood glucose (mg/dl) / 22.5

RESULTS

Blood sugar levels (mean ± SD) for both groups are presented in table 1. The difference between two groups was very highly significant (p<0.001). Fasting insulin levels (table 2) for non obese and obese were 10.1 ± 2.1 and 17.3 ± 4.6 µIU/L respectively and the difference was very highly significant (p-value <0.001). Insulin resistance, evaluated on the basis of HOMA-IR is shown in table 2. HOMA-IR level for non obese was 2.26 ± 0.58 and that for obese, 4.2 ± 1.3 with highly significant difference between two groups (p-value <0.001). Insulin resistance is represented by HOMA-IR value of >2.925 (figure 1). Eighty eight percent cases among obese subjects had HOMA-IR > 2.925 and there were 88.6% cases among non obese who had their HOMA-IR levels < 2.925.

Table 1: Serum fasting BSL in non obese and obese groups

Variable	Non Obese n=44 mean ± SD	Obese n=44 mean ± SD	p-value
BSL (mg/dl)	90.2± 7.2	97.2± 7.1	<0.001***

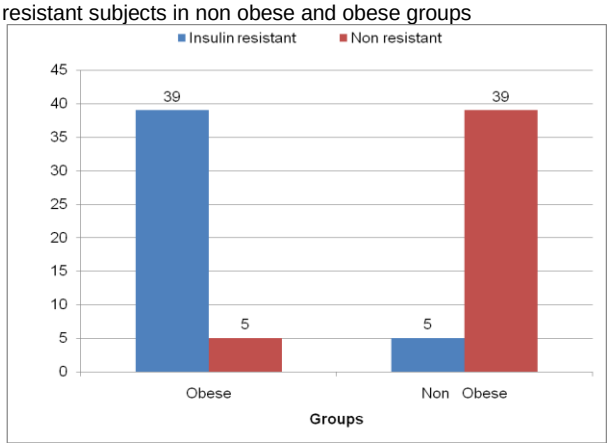
***=very highly significant
Results are expressed as mean±SD.

Table 2: Serum Insulin and HOMA-IR levels in non obese and obese groups

Variable	Non Obese n=44 mean ± SD	Obese n=44 mean ± SD	p-value
Insulin (µIU/ml)	10.1 ± 2.1	17.3 ± 4.6	<0.001***
HOMA-IR	2.26 ± 0.58	4.20 ± 1.39	<0.001***

*** = very highly significant

Fig. 1: Comparison of number of insulin resistant and non insulin resistant subjects in non obese and obese groups



DISCUSSION

Polycystic ovarian syndrome is an endocrine disorder but environmental factors like diet and lifestyle may also influence the presentation of this disease.The polycystic ovary syndrome (PCOS) and the metabolic syndrome (MS) are common disorders that share many characteristics, particularly abdominal obesity and insulin resistance[16]. Insulin resistance and compensatory hyperinsulinemia are considered as pathogenic factors for polycystic ovarian syndrome as well as metabolic syndrome.

In present study, it was found that only two cases of obese polycystic ovarian syndrome patients (4.5%) had abnormal blood glucose levels. There were high insulin levels and HOMA-IR values which showed the presence of insulin resistance. Insulin resistance in women with polycystic ovarian syndrome was found to be enhanced by obesity.

In non-obese women, the presence of insulin resistance is controversial; in fact some data suggests that there is no insulin resistance in these patients however majority of obese polycystic ovarian syndrome patients appear to manifest insulin resistance[17].In the present study obese women with polycystic ovarian syndrome showed significantly higher fasting levels of serum insulin as

compared to non-obese patients. Moreover, obese women with polycystic ovarian syndrome had increased insulin resistance as compared to non-obese women. In accordance with this,many studiesalso showed increased incidence of insulin resistance in obese patients[18,19]. Similar findings were observed by Barber et al. who reported insulin resistance in 50-90% of obese patients and treatment of this symptom by insulin sensitizing drugs resulted in improvement of many clinical features of polycystic ovarian syndrome[17]. Contrary to this, Kaira et al. in an Indian study reported increased insulin resistance in 50 out of 65 polycystic ovarian syndrome patients in the absence of obesity[20]. Oh et al. also observed insulin resistance in non-obese women with polycystic ovarian syndrome[21].

Although increased insulin resistance as shown by HOMA-IR values points towards an increased risk of type 2 diabetes mellitus in these women but paradoxically, fasting glucose levels did not fulfill the criterion for metabolic syndrome in this study. This shows that polycystic ovarian syndrome patientshave significant insulin resistance and are more prone to develop diabetes mellitus in later age but glucose levels did not coincide with these findings so further studies are required to be conducted in this regard.

In this study, decreased insulin resistance in non-obese group is probably because of the fact that in the absence of obesity the metabolic disturbance is not manifested properly. Similar findings were observed in a Saudi study performed by Ardawi et al who reported increased HOMA-IR in obese women as compared to non-obese women with polycystic ovarian syndrome[22].

CONCLUSIONS

Polycystic ovarian syndrome was found to be associated with components of metabolic syndrome including insulin resistance in obese as well as non-obese subjects. However, when comparison was done between two groups, it was found that all the parameters of metabolic syndrome were more prevalent in obese as compared to non-obese subjects, showing that obesity has much influence in causation of these abnormalities.

REFERENCES

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004; 89(6): 2745-9.
2. Carmina E, Lobo RA. Polycystic ovary syndrome: Arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab 1999; 84(6): 1897-9.
3. Bonnar J, Dunlop W. Recent advances in obstetrics and gynecology. 1st edn., Dublin 2003. Hodder Education Publisher.
4. Ali AT. Polycystic ovary syndrome and metabolic syndrome. Ceska Gynekol 2015; 80(4): 279-89.
5. Vignesh J, Mohan V. Polycystic ovary syndrome: A component of metabolic syndrome? J Postgrad Med2007;53: 128-33.
6. Haq F, Aftab O, Rizvi J. Clinical, biochemical and ultrasonographic features of infertile women with polycystic ovarian syndrome.JCPSP2007;17(2): 76-80.
7. Coviello AD, Sam S, Legro RS, Dunaif A. High prevalence of metabolic syndrome in first degree male relatives of women with polycystic ovary syndrome is related to high rates of obesity. J ClinEndocrinolMetab2009;94(11): 4361-6.
8. Rahmanpour H, Jamal L, Seyed Mousavinasab N, Esmailzadeh A, Azarkhish K. Association between polycystic ovarian syndrome, overweight, and metabolic Syndrome in adolescents. J Pediatr Adolesc Gynecol 2012; 25(3): 208-12.
9. Hoegar K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. J Clin Endocrinol Metab 2008; 93(11): 4299-306.
10. Wijeyaratne CN. Clinical manifestations and insulin resistance in polycystic ovary syndrome among South Asians and Caucasians: is there a difference? ClinEndocrinolOxf2002; 57(3): 343-50.
11. Bhattacharya SM. Metabolic syndrome in females with polycystic ovarian syndrome and international diabetes federation criteria. J ObstetGynaecol Res2008; 34(1): 62-6.
12. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Leufent C. NHLBI/AHA Conference proceedings. Circulation2004; 109: 433-8.
13. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Alexandraki KI. Early onset adiposity: A pathway to polycystic ovary syndrome in adolescent? Hormone 2007; 6(3): 210-7.
14. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in the women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005; 90(4): 1929-35.
15. Ganie MA, Kalra S. Polycystic ovary syndrome - A metabolic malady, the mother of all lifestyle disorders in women - can Indian health budget tackle it in future? Indian J EndocrMetab2011;15: 239-41.
16. Panidis D, Macut D, Tziomalos K, Papadakis E, Mikhailidis K, Kandaraki EA. Prevalence of metabolic syndrome in women with polycystic ovary syndrome. ClinEndocrinol2013;75(4): 586–92.
17. Barber TM, Franks S. The link between polycystic ovary syndrome and both type 1 and type 2 diabetes mellitus. Women's Health 2012; 8(2): 147-54.
18. Cussons AJ, Watts GF, Burke V, Shaw JE, Zimmet PZ, Stuckey BGA. Cardiometabolic risk in polycystic ovary syndrome: a comparison of different approaches to define the metabolic syndrome. Hum Reprod2008; 23(10): 2352–8.
19. Faloia E, Canibus P, Gatti C, Frezza F, Santangelo M, Garrapa GG. Body composition, fat distribution and metabolic characteristics in lean and obese women with polycystic ovary syndrome. J Endocrinol Invest2004; 27(5): 424-9.
20. Kaira A, Nair S, Rai L. Association of obesity and insulin resistance with dyslipidemia in Indian women with polycystic ovarian syndrome. Indian J Med Sci2006; 60: 447-53.
21. Oh JY, Sung YA, Lee HJ, Oh JY, Chong YW Pak H. Optimal waist circumference for prediction of metabolic syndrome in young Korean women with polycystic ovary syndrome. Obesity2010; 18(3): 593-7.
22. Ardawi MSM, Rouzi AA. Plasma adiponectin and insulin resistance in women with polycystic ovarian syndrome. FertilSteril2005; 83(6): 1708-16.