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Original Research Article

Role of leutenising hormone LH and insulin resistance in polycystic ovarian syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder seen in pre-menopausal women, affecting 5-10% of this population. It is characterized by menstrual irregularities and clinical hyperandrogenism such as hirsutism, seborrhoea and acne. PCOS women have insulin resistance, which results in compensatory hyperinsulinemia. A number of findings suggest that hyperinsulinemia may play a central role in the development of hyperandrogenism. This study is under taken to measure insulin resistance and leutenising hormone (LH) in PCOS patients and to see the relationship of insulin resistance with leutenising hormone (LH).
Methods: Case control study was done taking 60 women PCOS and 60 age matched healthy women as controls. In all the subjects, concentrations of fasting plasma glucose estimated using enzymatic methods in semiautoanalyser. Fasting serum insulin and leutenising hormone (LH) measured by CLIA using Lumax-CLIA microplate reader. HOMA IR was calculated from estimated parameters.
Results: The concentration of fasting serum insulin,fasting plasma glucose,HOMA –IR and leutenising hormone(LH) in controls are 9.33±3.08 µIU/ml,94.38±10.36mg/dl,12.16±0.67and 4.67±1.94 mIU/ml respectively; in PCOS cases they are 24.50±10.03µIU/ml,114.20±30.38 mg/dl,7.29±4.08 and 15.75±7.51 mIU/ml respectively. The mean concentrations of all the parameters were significantly (p value<0.05) increased in women with polycystic ovarian syndrome when compared with healthy women.
Conclusions: This study shows that 75% of pcos women were insulin resistant and HOMA IR shows a positive correlation (r value 0.48, p<0.05) with serum leutenising hormone(LH).

Keywords: Insulin resistance, Luteinizing hormone, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome is a highly prevalent hormonal and metabolic disorder among reproductive aged women worldwide. According to Rotterdam criteria polycystic ovarian syndrome is defined as having any two of following:

- Oligo/anovulation
- Clinical/biochemical signs of hyperandrogenism
- Polycystic ovaries by scan with exclusion of other related disorder.[1]

Several studies have suggested a prevalence of PCOS of between 5% and 10 % in women of reproductive age group. Polycystic ovary alone is found in 20-25% of women.[2] The prevalence of PCOS varies with ethnicity or race. It was reported in 6.6% in South Eastern United

States, 6.8% in Geece, 6.5% in Spain, 13% among Mexican American Women, and 52% among female South Asian immigrants of Britain.[3] PCOS is a heterogenous disorder for which several pathogenic mechanisms have been proposed. The main mechanism is abnormal gonadotropin secretion, with excess circulating LH and low FSH. Hypersecretion of androgen by ovarian and adrenal gland which provide substrate for peripheral aromatisation to estrogen also play role in development of PCOS.[4] FSH and LH secretion patterns reflects the integration of sensitive complex hypothalamic, pituitary, and peripheral signals. GnRH pulse amplitude and frequency determine the physiologic patterns of LH and FSH secretion. Decreasing GnRH pulse frequency enhances LH pulse amplitudes.[5]

PCOS women have insulin resistance. Insulin resistance, defined as an impaired biological response to insulin, along with its compensatory hyperinsulinemia .The defect in insulin action in PCOS appears to be at the post binding level which involves glucose transport.[6] These are hallmarks of polycystic ovarian syndrome, which puts women with polycystic ovarian syndrome at an increased risk of impaired glucose tolerance and T2DM.[7,8] This study is undertaken to find out prevalence of insulin resistance in polycystic ovarian syndrome patients. There are not many studies to evaluate relationship between insulin resistance and luteinizing hormone (LH). Hence, we would like to evaluate relationship of insulin resistance with luteinizing hormone in polycystic ovarian syndrome patients. We hypothesize that correlation exist between insulin resistance and luteinizing hormone in polycystic ovarian syndrome patients.

METHODS

A study will be carried out for a period of one year. The patients will be selected from Chigateri General Hospital and Bapuji Hospital, Davangere (both hospitals are attached to the teaching institute JJM Medical College, Davangere) and private hospital in and around JJMMC Davangere. Study will be carried out in clinically 60 diagnosed cases of polycystic ovarian syndrome and 60 age matched controls will be selected based on inclusion and exclusion criteria

Inclusion criteria

Cases; patients between age 17-36yrs diagnosed as polycystic ovarian syndrome having clinical features: oligomenorrea (35days), amenorrea (6months), hyperandrogenisum features like acne, hirsuitism, and diagnosed polycystic ovaries by ultrasound. Controls; 17-36 years females having normal menstrual cycle.

Exclusion criteria

Patients having history of diabetes mellitus, impaired glucose tolerance, Pregnancy, breast feeding, non-fasting, Patients with untreated hypothyroidism, those on drug treatment like antihypertensive, antiplatelet, lipid lowering agents, drug affecting glucose and lipid metabolism, congenital adrenal hyperplasia, cushing syndrome, ovarian/adrenal androgen secreting tumors.

Ethical clearance obtained from institutional ethics comity. After taking informed consent, under all aseptic precautions about 5 ml of venous blood will be collected in a sterile bulb after overnight fasting of 12 hours. Sample is collected during follicular phase of menstrual cycle. 2ml will be collected in EDTA vial (for plasma), 3ml in plain vial for (for serum), it will be subjected for centrifugation, serum and plasma will be separated. Insulin and luteinizing hormone (LH) were estimated from serum and fasting glucose from plasma. Fasting plasma glucose measured by GOD POD method by Erba mannheim chem5 plus Semi Auto-analyzer". Normal value of fasting plasma glucose is 70-110mg/dl.

Fasting insulin and luteinizing hormone (LH)estimated by chemiluminescence immunoassay. Normal value of fasting insulin is 5-25µIU/ml. Normal value of luteinizing hormone (LH) in follicular phase is 0.5-10.5 mIU/ml. Calculation of insulin resistance by using HOMA model (HOMA -IR).[9]

HOMA-IR = (Fasting plasma glucose in mg/dl x fasting serum insulin in µiu/ml)/405

The subject is considered to have insulin resistance if HOMA-IR value is more than 2.7.

Statistical analysis

Statistical analysis was done using SPSS software, version 17.0. Descriptive data were presented as mean ± SD and range values. Unpaired student t test used to compare between cases and controls. Relationship between insulin resistance and serum luteinizing hormone (LH) was assessed by Pearson's correlation coefficient. For all the tests, the probability value (p-value) of less than 0.05 was considered statistically significant.

RESULTS

In the present study, a total number of 120 subjects were included. They were divided into 2 Groups: Controls-It consisted of 60 healthy women Cases-It consist of 60 PCOS cases

The mean age was not statistically significant. The concentration of fasting serum insulin, fasting plasma glucose, HOMA-IR and leutenising hormone (LH) in controls are 9.33±3.08 µIU/ml, 94.38±10.36mg/dl, 12.16±0.67and 4.67±1.94 mIU/ml respectively; in PCOS cases they are 24.50±10.03µIU/ml, 114.20±30.38 mg/dl, 7.29±4.08 and 15.75±7.51 mIU/ml respectively. The mean concentrations of all the parameters were significantly (p value <0.05) increased in women with

polycystic ovarian syndrome when compared with healthy women (Table 1).

Table 1: Comparison of fasting plasma glucose, fasting insulin, luteinizing hormone (LH) and insulin resistance in study groups. results expressed as mean ± SD.

Parameter	PCOS cases	Controls	P value
Mean age	29.42±6.88	27.72±6.66	0.17
Fasting serum insulin (µIU/ml)	24.50±10.03	9.33 ±3.08	<0.05
Fasting plasma glucose mg/dl	114.20±30.38	94.38±10.36	<0.05
HOMA IR	7.29±4.08	2.16±0.67	<0.05
Luteinizing hormone (LH) mIU/ml	15.75±7.51	4.67±1.94	<0.05

Prevalence of insulin resistance in PCOS cases

In insulin sensitive indivials HOMA IR value found to be <2.77. In this study, out of 60 PCOS cases, 45 cases HOMA IR value found to be more then 2.77. So prevalance of insulin resistant cases in PCOS cases in this study is 45/60 i.e. 75%. There is positive correlation (r value 0.48) between HOMA IR levels with serum luteinizing hormone (LH) (Table 2).

Table 2: Correlation of insulin resistance with luteinizing hormone (LH).

Variables	r value	p value
Serum luteinizing hormone (LH)	0.48	<0.05

DISCUSSION

Polycystic ovarian syndrome (PCOS) is a heterogeneous disorder of unknown aetiology affecting 5-10% of women of reproductive age. It is a disorder that affects the reproductive, endocrine and metabolic functions and is the leading cause of chronic anovulation leading to infertility. Also, it is associated with obesity, insulin resistance; dyslipidemia and endothelial dysfunction.[10] a number of findings suggest that hyperinsulinemia may play a central role in the development of hyperandrogenism in pcos patients.[11]

Prevalence in this study is 45/60 i.e. 75%. This is similar to anuradhaclara et al where prevalence of IR in PCOS found to be 76.9 % and is in consistent with previous studies that showed Indian PCOS women to be more insulin resistant then there white counterparts.[12,3] Prevalence of insulin resistance differs by method used to estimate IR. In a study done by pikee saxena et al prevalence found to be 88%.[13] They used 2-hour post glucose insulin level to identify IR. Presence of insulin resistance is quoted as the main reason for elevation of fasting glucose levels in these studies. S pikee et al found that in patients with normal glucose tolerance, values of glucose remain in the normal range due to adequate insulin response.[13] A woman with IR, normal glycemic levels may be noticed after a glucose challenge because the pancreas will have to secrete excess insulin in order to keep the blood sugar in the normal range. However, with time the β-cells become increasingly dysfunctional and fails to secrete enough insulin to correct the prevailing hyperglycemia, resulting in increased glucose level.[13]

In polycystic ovarian syndrome patients, there is relative inefficiency of insulin receptors binding to insulin which leads to improper transfer of glucose to intracellular compartment and this result in relative hyperglycemia, in spite of increased insulin producing beta cells. In polycystic ovarian syndrome adipocytes there is significant decrease in number of GLUT4 glucose transporters.[14] in cultured skin fibroblast of women with PCOS, impaired insulin action on glycogen synthesis is associated with constitutively increased insulin receptor beta subunit serine phosphorylation and decreased insulin receptor tyrosine kinase activity. A serine kinase extrinsic to receptor is responsible for these abnormalities.[15]

In present study, we found that the mean serum levels of LH are significantly increased in subjects with PCOS when compared to healthy controls. It is in accordance to the studies carried out by Mutib M T et al, Feuser C et al, Fulghesu A M et al and Cheung L et al.[16-19] Anovulation in women with pcos is characterised by inappropriate gonadotropin secretion. Alteration in gonadotropin releasing hormone pulsatility leads to preferential production of luteinizing hormone (LH) compared with follicle stimulating hormone (FSH) Hypothalamic dysfunction may be primary cause or secondary to abnormal steroid feedback. In either case serum LH level rise and increased levels are observed clinically in approximately 50% of affected women.[1]

It is mainly because of GnRH dysregulation. The abnormal secretion of ovarian androstenidione is seems to be intrinsic property of PCOS theca /granulose cells. A key step in androgen formation is regulation of p450c17 enzyme. Activation of this enzyme in ovary or adrenal cortex is regulated by number of hormones including insulin, LH and IGFs. Androstenidione can augments pituitary sensitivity to GNRH both by direct action on gonadotropin synthesis and by enhancing GNRH induced GNRH receptors. It has been postulated that altered input to GNRH neuronal system by insulin and or sex steroid may induce dysregulation of GNRH pulse generator activities.[16] However, mechanism of neuroendocrine dysfunction may be due to chronically elevated level of estrone, a weak estrogen aromatized peripherally from androstenedion, which is not counteracted by progesterone so uncoupling hypothalamic estradiol inhibition by elevated ovarian androstenidion.

At particular threshold this uncoupling is associated with estradiol related sensitization of pituitary LH release and hence increases LH secretion. Chronic LH stimulation in PCOS induces sustained hyper secretion of androgens by the theca compartment.[17] LH plays a critical role in the folliculogenesis. LH promotes the secretion of androgens by ovarian theca cells, which may result in follicular maturation arrest.[20]

Luteal cell LH receptors signal to enhance cAMP levels and induce cholesterol availability for ovarian steroid genesis. The StAR (steroidogenic acute regulatory) protein is induced by LH and mediates cholesterol delivery to the inner membrane. LH enhances cytochrome P450-linked enzyme activity to synthesize pregnenolone and induces 3b-hydroxysteroid dehydrogenase, 17a-hydroxylase, and 17, 20-lyase synthesis.[1] LH enhances theca cell steroidogenesis through the cAMP-protein kinase A pathway. Insulin regulates steroidogenesis by acting through its own receptor. In classical insulin-responsive tissues, insulin's actions are mediated via three major pathways: the phosphatidyl-inositol 3-kinase (PI-3K) pathway, implicated in the metabolic effects of insulin; the MAPK pathway, responsible for the mitogenic effects of insulin; and the protein kinase C (PKC) pathway, which can also be activated via G protein activation of phospholipase C.[21]

Because LH and insulin act physiologically via distinct intracellular signaling mechanisms, their synergistic enhancement of theca cell steroidogenesis likely entails important interactions between pathways of these two-respective hormone. It has been shown that insulin significantly increases LH-driven cAMP accumulation in theca. This insulin-stimulated increase in cAMP could be induced through PI-3K and/or PKC.[21] These observations provide a molecular basis to the hypothesis of significant co relation between the LH and insulin signaling pathways and support the possibility of a defect in women with PCOS affecting both insulin and LH-stimulated ovarian androgen production as well as synergistic responses.

CONCLUSION

The study shows significantly increased concentrations of fasting plasma glucose, insulin, luteinizing hormone (LH) and HOMA IR in pcos patients when compared to healthy women. This signifies presence of insulin resistance in women with PCOS. Our study shows positive correlation between insulin resistance and luteinizing hormone (LH). Insulin can stimulate ovarian androgen production in women with PCOS. Insulin resistance may be the first important marker of metabolic disease in PCOS women, who are at risk of development of type 2 diabetes, obesity, hypertension, dyslipidemia and coronary artery disease. Women develop PCOS because of a hypersensitivity of their intraovarian insulin androgen signalling pathway Hence PCOS patients should be screened for insulin resistance. By giving appropriate treatment for insulin resistance in pcos women, we can lower androgen level and improve ovulatory function.

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