Can serum leptin be a predictor of cardiovascular risk in non-obese polycystic ovarian syndrome?

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Abstract

Introduction: Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of unknown etiology affecting approximately 7% of the women in reproductive age.It is generally characterized by menstrual irregularity, subfertility, hirsutism, acne and abnormal biochemistry with raised serum testosterone, androstenedione, and insulin and luteinizing hormone levels.Leptin regulates energy homeostasis, neuroendocrine function, and metabolism. There is a direct relationship that exists between serum leptin and insulin resistance which forms a traditional risk factor for cardiovascular risks mainly including atherosclerotic vascular disease.

Material and Methods: A group of 30 non-obese women suffering from polycystic ovarian syndrome were considered. Their blood samples were collected and tested for serum leptin, insulin and blood glucose. The values were correlated with BMI (body mass index) values and the conclusions were made.

Result: Mean serum leptin level recorded was 4.929 ng/ml and the HOMA value ranged from 1.5- 3.0. The Pearson's Correlation Coefficient was +1.00, which indicates a positive relationship between the two values.

Conclusion: We report that there is a direct relationship between serum leptin levels in females suffering from polycystic ovarian disorder. This information can be used to assess the risk of cardiovascular disorders in these particular subjects.

Keywords: Polycystic ovarian syndrome, Serum leptin, insulin, Cardiovascular risk.

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of unknown etiology affecting approximately 7% of the women in reproductive age.[1] No community based prevalence data is available for PCOS. It is generally characterized by menstrual irregularity, subfertility, hirsutism, acne and abnormal biochemistry with raised serum testosterone, androstenedione, and insulin and luteinizing hormone levels.[2] PCOS has a variety of predisposing factors which are classified as biochemical and clinical. The biochemical factors include- BMI is a key risk factor associated with the incidence of PCOS (higher BMI has been implicated as an important indicative marker of PCOS status.) In women with PCOS, changes in BMI during adolescence are positively associated with changes in waist circumference (p < 0.0001), low density lipoprotein-cholesterol, triglycerides, and systolic blood pressure. Development of insulin resistance (IR) and dysregulation of lipid metabolism are seen even in the early stages of PCOS. Significantly higher IR (fasting serum insulin) is observed in patients with PCOS with apparently normal oral glucose tolerance test (OGTT). Presence of family history of PCOS or diabetes or an inadequate lifestyle have also been shown to be important risk factors for incidence of PCOS. In addition, development of clinical features of PCOS is often preceded by a history of weight gain, and factors independently associated with BMI: higher energy intake and glycemic index, low physical activity, smoking, alcohol intake.[3]

PCOS is of four types depending upon the symptoms of the patient- insulin resistant PCOS, pill induced PCOS or post pill PCOS, inflammatory PCOS (chronic immune activation due to stress or environmental toxins, hidden cause PCOS (maybe due to thyroid diseases, vegetarian diet, iodine deficiency, artificial sweeteners etc.) This research study deals with the correlation of serum leptin and polycystic ovarian disorder which is of the insulin-resistant type. The woman who has PCOS would more likelydevelop the complications like infertility, breast cancer (slightly increased risk) and endometrial cancer.[4]

Leptin, is a 167-amino-acid product of the human leptin gene, Leptin regulates energy homeostasis, neuroendocrine function, and metabolism. Circulating leptin levels reflect primarily the amount of energy stored in fat and secondarily acute changes in caloric intake.[5] Insulin resistance and hyperinsulinemia may also be factors that affect serum leptin levels as shown in some studies. It had been shown that insulin directly induces leptin mRNA in adipocytes in vitro, suggesting that insulin may stimulate leptin secretion.[6] Serum leptin is also a direct marker of cardiovascular diseases because it has been correlated with increased vascular calcification which is an emerging factor in the process of atherosclerotic vascular disease. Insulin resistance, systemic hypertension, and hypercholesterolemia all contribute independently to vascular endothelial dysfunction that promotes atherosclerosis and coronary heart disease. Reciprocal relationships between endothelial dysfunction and insulin resistance are characterized by impaired insulin-

stimulated nitric oxide (NO) production from endothelium that decreases blood flow to insulin target tissues.[7] Hence, there seems a direct relationship that exists between serum leptin and insulin resistance which forms a traditional risk factor for cardiovascular risks mainly including atherosclerotic vascular disease. The aims and objectives of the research are to summarize promising areas of investigation in patients suffering from polycystic ovarian syndrome and stimulate further research in this particular field.

1. To determine the levels of serum leptin in non-obese women in the reproductive age suffering from polycystic ovarian syndrome.
2. To determine the levels of insulin resistance in non-obese women suffering from PCOS.
3. To correlate whether serum leptin is associated with insulin resistance and hence, the subsequent risk of cardiovascular disorders in women suffering from PCOS

Materials and Methods

Study was done by universal sampling method. Approval was taken from the Institutional Ethics Committee. After the approval, informed consent of the patients was taken before carrying out the study any further. The study was carried out at the biochemistry department of N.K.P Salve Institute of Medical Sciences and Research Centre. It was carried out over a time period of 2 months, since it was short term studentship proposal.30 non-obese women suffering from PCOS were selected based on the inclusion and exclusion criteria listed below. Patients of the age group 15-45 years who are symptomatic cases of PCOS with a history of menstrual irregularity, subfertility, acne who are non-obese women with BMI <30. All participants were willing to participate without history or signs and symptoms of any major illness. Patients with any chronic inflammatory disease, type.2 diabetes mellitus, IHD, hypothyroidism, nephritic syndrome, any patient with obesity i.e. with BMI >30 were excluded from the study. Any patients with personal or familial history of hyperlipidemia, females on any systemic drug therapy in the recent month were also excluded from the study. Any patient not willing to cooperate after initially signing the informed consent form was allowed to withdraw from the study as per their will.

5 ml of fasting venous blood was collected in a plain bulb. The venous blood sample was analyzed for fasting glucose levels by Hexokinase kit method. The venous blood sample was centrifuged for the separation of serum. the serum was then analyzed for leptin and insulin levels by ELISA kits. Insulin resistance was determined by HOMA index.

Statistical Analysis

A frequency distribution table was made from which the arithmetic mean for the levels of serum leptin has been calculated. This was done by adding all the values and dividing them by the total number of readings using Epi Info version7.1.1.1.14 statistical software. The insulin resistance is calculated by HOMA (Homeostatic model assessment) which assess beta-cell function and IR from basal (fasting) glucose concentrations. Correlation between the two variables was studied using Pearson's correlation coefficient test.

Results

Table 1: Leptin levels in the non-obese females suffering from Polycystic Ovarian syndrome

Serum Leptin Level Range	No. of Subjects
0-3 ng/ml	11
3-6 ng/ml	11
6-9 ng/ml	3
9-12 ng/ml	4
>12 ng/ml	1

Table 2: Insulin resistance levels in the non-obese females suffering from Polycystic Ovarian syndrome

Homa Values Range	No. of Subjects
0-0.5	0
0.5-1.0	0
1.0-1.5	0
1.5-2.0	22
2.0-2.5	7
2.5-3.0	1

As depicted in table 1 the serum leptin levels in patients as recorded by the process of ELISA when correlated with BMI i.e. body mass index in the patients were slightly increased than the normal. The mean serum leptin level (n=30) is 4.929 ng/ml.

As depiocted in table 2, the Pearson's Correlation Coefficient for the samples is- +1.00

Since the value of Pearson's Correlation Coefficient is more than zero, it indicates a positive relationship between the serum leptin levels and the insulin resistance levels.

Discussion

It is long known that females in the menopausal age are more susceptible to cardiovascular episodes. Proposed mechanisms of this association include the sudden decrease of estrogen exposure along with other factors, contributing to the increased CVD risk with putative effects on vasculature and cardiac function.[8,9]

Serum leptin levels are directly proportional with BMI. They are significantly increased in obese women. However, the aim of the project undertaken was to prove the relationship between the serum leptin levels in non-obese females suffering from polycystic ovarian syndrome. Although the levels fall within the normal range, they are increased when compared to individuals not suffering

from PCOS of comparative BMI.

Leptin, a protein secreted by adipocytes, suppresses an individual's appetite and promotes energy expenditure. Serum leptin levels are elevated in obese patients, who are considered leptin resistant.[10] Hyperleptinemia seems to be a positive risk factor for cardiovascular disease.[11-13] The study by Mukhtair Baig et al was aimed to investigate the levels of serum leptin in PCOS females and to correlate it with metabolic and hormonal parameters. There was no significant difference found in circulating leptin concentration between PCOS and normal subjects. Leptin levels in PCOS were related with metabolic impairments manifested by disturbance in FBG (fasting blood glucose) levels and impairment of reproductive functions in terms of reduced E2 (prostaglandin E2) secretion.[2] The study by Jahanfar.S. et al states thatpolycystic ovary syndrome (PCOS) is a common endocrinopathy with symptoms such as obesity, insulin resistance and hyperandrogenemia. PCOS might be the result of a genetic disorder. Genetic discrepancy in the production of leptin, a product of the obesity gene, may lead to various endocrinopathies such as PCOS. The objective of his study was first, to ascertain the incidence of PCOS, using the gold standard; second, to ascertain the genetic property of leptin; and third, to evaluate the association between leptin concentration and PCOS.[7]

Although some studies have found leptin levels to be elevated in PCOS women compared to controls,[14,15] the general consensus reported by the majority of published studies is that there is only a mild difference in circulating leptin levels in PCOS subjects in comparison to BMI-matched controls.[16-24] Leptin independently correlates with insulin resistance which indicates that leptin plays a significant role in insulin resistance is PCOS patients.[25]

Hence, it is important to consider the insulin resistant levels in this case because serum leptin is responsible for insulin resistance which in turn points towards increased risk of cardiovascular diseases.

Conclusion

We report that there is a direct relationship between serum leptin levels in females suffering from polycystic ovarian disorder. This accounts for insulin resistance in the subjects. This information can be used to assess the risk of cardiovascular disorders in these particular subjects.

Summary

Our study assessed the role of serum leptin levels in females suffering from polycystic ovarian syndrome and the direct risk of cardiovascular disorders. However, further studies with more samples along with multiple parameters for assessing the cardiovascular risk in PCOS subjects should be taken into consideration.

Conflict of Interest: None.

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