Serum leptin level in women with polycystic ovarian syndrome

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Abstract:

Background:

Leptin, a key hormone in energy homeostasis and neuroendocrine function, has a permissive role in the pathogenesis of reproductive dysfunction.

Objective:

To assess the role of serum leptin in women with PCOS and to evaluate leptin and insulin levels in PCOS women before and after treatment with metformin.

Materials and Methods:

Sixty women of reproductive age (18- 38years) were allocated to four groups: 15 obese women with PCOS (BMI >30 kg/m^2), 15 obese controls, 15 non-obese women with PCOS (BMI 18 -30 kg/m^2), and 15 non-obese controls. Serum leptin and insulin levels were measured and compared between case and control subjects also comparison done pretreatment and after treatment with metformin.

Results:

There was a significant increase in leptin in non-obese PCOS group(8.2± 2.73) compared to non-obese control (5.64± 1.43), (P value=0.0032), insulin level was significantly higher in PCOS group (15.87 ±6.65) than control (5.47 ±1.68), (P value<0.001). There was significant decrease in BMI ,leptin and insulin levels after 12 month of metformin treatment in obese and non-obese PCOS subjects.

Conclusion:

Leptin level increased remarkably with increasing body weight and it is higher in non-obese PCOS women in comparison with non-obese healthy women.

.Key words : PCOS, Leptin, Metformin

Introduction

Polycystic ovarian syndrome is the most common endocrinopathy in women, affecting 5–10% of women of reproductive age[1] with onset manifesting as early as puberty.(1)

The principal features of PCOS are anovulation, resulting in irregular menstruation, amenorrhea, ovulation-related infertility, and polycystic ovaries; excessive amounts or effects of androgenic (masculinizing) hormones, resulting in acne and hirsutism; and insulin resistance.[2]

Because of the diversity of clinical and metabolic findings in PCOS, there has been great debate as to whether it represents a single disorder or multiple associated pathologic conditions.The current understanding is that PCOS is not only a gynecological condition but a metabolic syndrome with associated disorders such as insulin resistance and dyslipidemia[3]. Infertility is related to insulin resistance which disturbs the hormonal milieu in these women.

Approximately 50% of women with PCOS are overweight (BMI > 25 kg/m2) or obese (BMI > 30 kg/m2). Women with PCOS usually have so-called central obesity or upper-body obesity, and therefore tend to have an increased waist-hip ratio (WHR), even among subjects of normal weight[4].

Leptin, a key hormone in energy homeostasis and neuroendocrine

function, has a permissive role in the pathogenesis of reproductive dysfunction. It is the product of the ob gene secreted from adipose tissue which signals the amount of energy stores to the brain and is implicated in the regulation of food intake and energy balance.[5]

The very close association between hyperinsulinemia and hyperleptinemia suggests that expression of the (ob)gene, which codes for leptin, may be mediated by insulin both in humans and in rats[5]. In addition, it has been suggested that insulin indirectly regulates leptin secretion due to its trophic effect on the adipocytes[6].Thus, insulin, leptin, body weight, ovarian steroidogenesis and ovulation show complex interrelations. Leptin resistance was introduced in an apparent analogy with that of insulin resistance to explain why hyperleptinemia associated with obesity fails to correct the defect in energy balance and feeding behavior. [7]

Metformin is an antidiabetic drug with anorexigenic properties. It appears to affect ovarian function in a dual mode, through the alleviation of insulin resistance on ovary and through direct effect on ovary. It reduces CYP17 activity in theca cells and reduces steroidogenesis in women with PCOS[8].

The study aimed to assess the role of serum leptin in women with PCOS,to evaluate leptin levels in PCOS women before and after treatment with metformin (an insulin sensitizing agent) and to study the correlations between leptin and other hormonal parameters.

Materials and Methods

This prospective experimental study included 60 women of reproductive age (18- 38years) were allocated to four groups:15 obese women with PCOS (BMI >30 kg/m2),15 obese controls, 15 non-obese women with PCOS (BMI 1830- kg/m2), and 15 non-obese controls.

The controls were volunteers who freely agreed to participate in the study; they had regular cycle and received no treatment for a chronic illness. The diagnosis of PCOS was based on Rotterdam criteria which indicated PCOS to be present if 2 of 3 criteria are met in the female:

(1) Oligo-ovulation and/or anovulation.

(2) Excess androgen activity(clinical or biochemical).

(3) Polycystic ovaries on gynecological ultrasound (10 or more follicles in each ovary, each follicle measuring 2–9 mm in diameter).

The serum of patient was collected after an overnight fast of 10 -12 h, separated after centrifugation into two samples; the first sample was analyzed immediately for FSH ,LH ,Prolactin , Estradiol ,Testosterone and lipid profile. The second sample was stored at -20 c until a time of analysis of leptin and insulin using ELISA technique.

The PCOS patients received metformin tablet 500 mg twice daily (Glucophage® MERK-SERONA) and the above measures were repeated after 12 weeks (serum ,leptin, and insulin) and comparison done between the results before and after treatment with metformin.

Results

Figure (1) shows no significant increase in leptin level in obese PCOS (22.04 ±7.79 ng/ml) in comparison with age and BMI matched obese control group (24.29± 10.06 ng/ml), (P value =0.49), while a significant increase in insulin level noticed in obese PCOS (21.53± 13.52 mIU/ml) compared to obese control (8.79 ±3.21 mIU/ml), (p value =0.0014) as shown infigure (2).

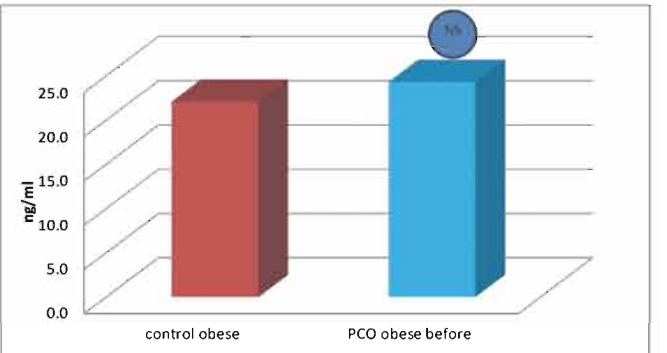

Fig. (1): Comparison of serum leptin concentration between control obese and PCO obese before treatment groups

NS:p value >0.05

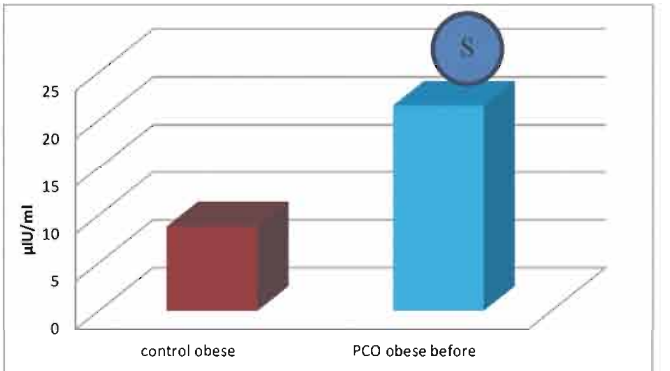

Fig. (2): Comparison of serum insulin concentration between control obese and PCO obese before treatment groups

Figure (3) displays significant increase in leptin level in non-obese PCOS group (8.2 ±2.73) in comparison with non-obese control (5.64 ±1.43), (P value =0.0032). Insulin level was significantly higher in PCOS (15.87± 6.65) than control (5.47 ±1.68),(P value <0.001) as demonstrated in figure (4).

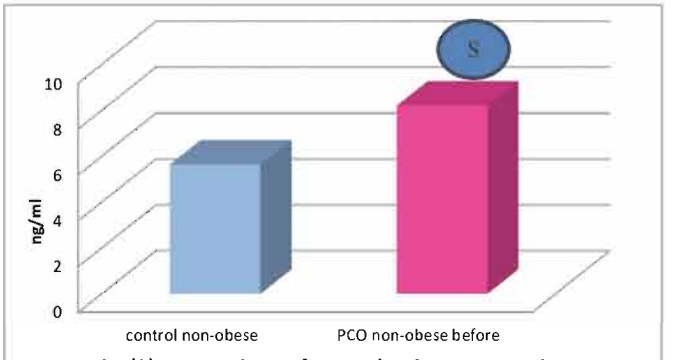

Fig. (3): Comparison of serum leptin concentration between control non-obese and PCO non-obese before treatment groups

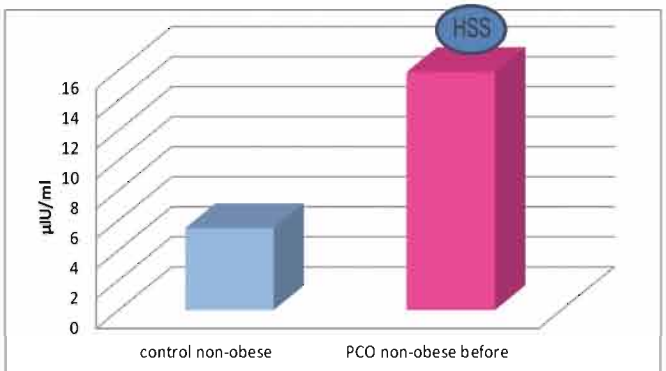

Fig. (4): Comparison of serum insulin concentration between control non-obese and PCO non-obese before treatment groups

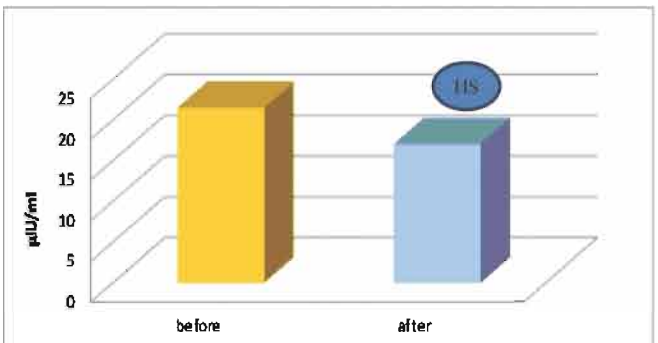

Fig.(7): Comparison of serum insulin concentration between PCO obese before treatment and after treatment groups

There was a significant decrease in BMI after 12 months metformin treatment in obese (33.32 ±2.66) compared to BMI before treatment (35.41± 3.47), P value =0.0032 as shown in figure. (5).

There was a significant decrease in leptin level in obese PCOS after treatment (20.7± 8.56 ng/ml) in comparison to that before treatment (24.29± 10.06 ng/ml) (p value< 0.05) as demonstrated in figure (6). Figure (7) shows a highly significant decrease in insulin levels in obese PCOS subjects after treatment (17.09 ±10.36uIU/ml) compared to that before treatment (21.53± 13.52 mIU/ml),(P value <0.001).

There was a highly significant decrease in BMI after 12 month metformin treatment in non-obese (21.952.05±Kg/m2) in comparison to BMI before treatment (23.572.02±Kg/m2), (P value<0.001) as noticed in figure (8).

There was a highly significant decrease in leptin level(6.272.17±ng/ml) observed in non-obese PCOS subjects after treatment compared to that before treatment (8.22.73±ng/ml)(p value <0.001) as shown in figure (9). Figure (10) demonstrates a highly significant decrease in insulin level in non-obese PCOS subjects after treatment (10.946.03± mIU/ml) compared to that before treatment (15.876.65±uIU/ml), (p value <0.001).

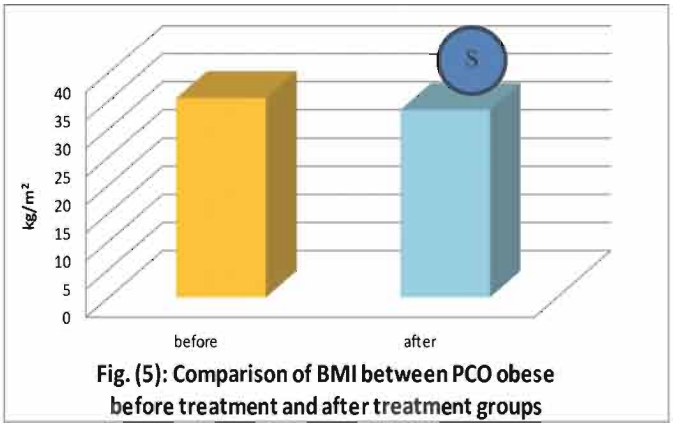

Fig. (5): Comparison of BMI between PCO obese before treatment and after treatment groups

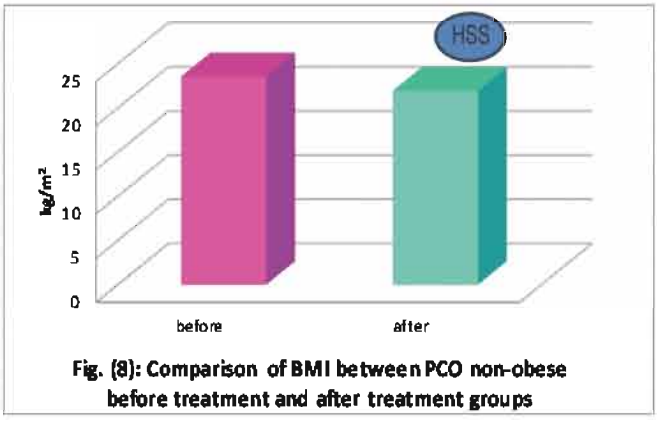

Fig. (8): Comparison of BMI between PCO non-obese before treatment and after treatment groups

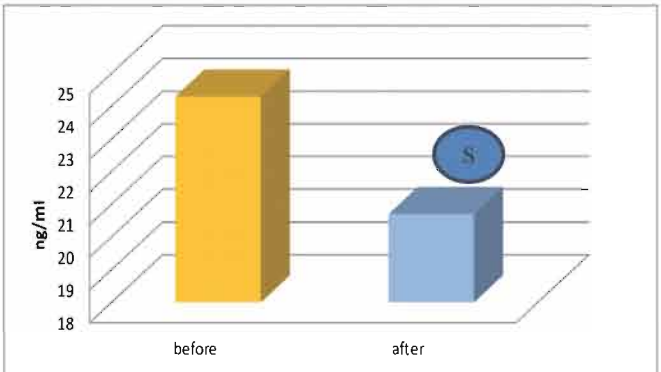

Fig. (6): Comparison of serum leptin concentration between PCO obese before treatment and after treatment groups

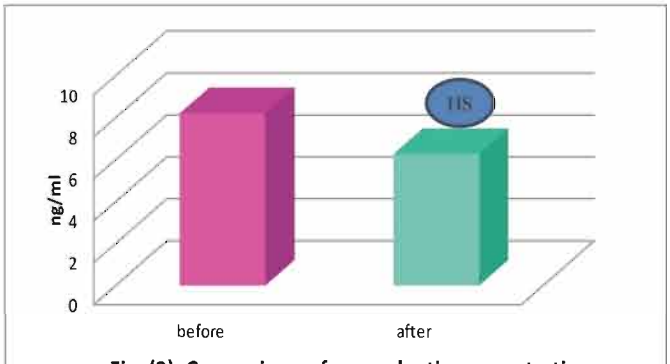

Fig. (9): Comparison of serum leptin concentration between PCO non-obese before treatment and after treatment groups

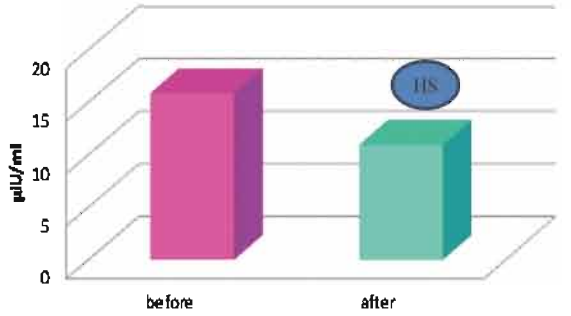

Fig. (10): Comparison of serum insulin concentration between PCO non-obese before treatment and after treatment groups

NS (Non-Significant): P value>0.05
S (significant):P value<0.05
HS (Highly Significant):P value<0.001

Discussion

Recent studies have shown that 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 and dyslipidemia.[9] [3] [10]

In the present study, BMI was significantly higher in non-obese PCOS subjects compared to non-obese control .Women suffering from PCOS shown to have higher amount of body fat compared to healthy women even when they are of normal weight [10]. BMI correlate with body fat and the obesity contributes to the manifestations of PCOS by increasing the magnitude of hyperandrogenism and the rates of anovulatory cycles.

Leptin levels are increased in obesity and may play a role in the development of insulin resistance and type 2 diabetes mellitus[11]. In the present study, leptin levels increased significantly with in both obese PCOS women and obese controls. The difference in mean leptin levels in non-obese and obese patients was highly significant.

In the current study there was no significant increase in leptin levels in obese PCOS when compared with obese control subjects, while a significant increase in leptin was found in non-obese PCOS subjects in comparison with Non-obese control.

Metformin treatment tends to restore the secretory capacity of neuropeptide Y(NPY) in obese women with PCOS offer a potential mechanism for the weight-reducing effect of metformin through normalization of appetite regulation in PCOS women.[12]

Metformin treatment resulted a significant decrease of serum leptin concentrations at three months of treatment, this is in accordance with previous studies[12] [13] [14]. Messenger RNA for leptin receptors has been found in both ovarian granulosa and theca cells[15], suggesting a possible direct role of leptin in ovarian function, as metformin may inhibit lipolysis in adipose tissue and thus play some role in the metabolism of fat cells[16], a direct effect of metformin on the secretion of leptin in fat tissue cannot be excluded.

During metformin treatment fasting serum insulin concentration decreased significantly and insulin sensitivity improved in obese and non-obese PCOS women, suggesting that the alleviation of hyperandrogenism brought about by metformin may be mediated by a decreased insulin action. Insulin stimulates leptin production *in vitro*[17] and in vivo[18].

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