Effect of Metformin Therapy on Reducing Leptin Resistance and Enhancing Ovulation in Women with Polycystic Ovary Syndrome

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Abstract

Background: The relation between insulin resistance ,leptin levels and other hormones in women with polycystic ovary syndrome(PCOS) is still controversial.Metformin therapy is proved effective in reducing insulin resistance and also in some studies it was seen to be effective in reducing leptin levels.

Objective: to study the effect of metformin on reducing leptin levels and enhancing ovulation in PCOS women.

Methods:metformin 500mg 3 times daily for 3 months was was given to 36 women with proved PCOS, in addition to that, other parameters were included.

Results:28 women out of 36(77.78%) showed an evidence of ovulation ovulation after 3 months of metformin therapy($p<0.01$) with significant reduction in leptin levels($p<0.001$).

Conclusion: it can be concluded that metformin can reduce leptin resistance and enhance ovulation in PCOS women.

Keywords: leptin, PCOS, metformin.

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Introduction

Polycystic ovary syndrome(PCOS) is a disorder characterized by chronic anovulation,hyperandrogenism, hyperinsulinemia, and often the presence of obesity.Women with PCOS have elevated serum luitinizing hormone(LH) and low or lower normal follicle stimulating hormone(FSH)
levels, with an increased ratio of LH to FSH.The increased LH secretion stimulates thecal cells in the ovary to produce an excess androgen and the androgen in turn, stimulates LH secretion, while the viscious circle goes on.

The androgen also inhibits production of sex hormone binding globulin(SHBG) resulting in excess free androgen responsible for hirsuitism.

Insulin resistance is an important component of PCOS and altered insulin action preceeds the increase in androgen in PCOS.The hyperinsulinemia may cause hyperandrogenism by binding insulin like growth factor1(IGF1) receptors in the ovary leading to increased androgen production by thecal cells[1].

Chronically, insulin exerts stimulating effect on adipocytes to increase leptin synthesis, a protein encoded by (ob gene). leptin in adipose tissue diminishes glucose oxidation, and lipogenesis while increasing fat utilization(anti-insulin effects [2,3].

Leptin may well play a role in the regulation of reproductive function in humans and other mammals, that is, animals and humans deficient in leptin are obese and hyperphagic and display a form of hypogonadotrophic hypogonadism[4].

a number of studies have failed to disclose a significant difference in fasting leptin concentrations between normal women and women with PCOS when matched for body mass index(BMI) or adiposity[5-7].

Leptin is thought to be part of the regulation of appetite, food intake and the lipid metabolism[8].

Obese humans present with hyperleptinemia as an indication of leptin resistanc which plays a major role in the pathogenesis of obesity[9].

Polycystic ovary syndrome is among the most common endocrine disorders, affecting more than 5% of women of reproductive age[10,11].

In lean subjects, leptin circulates predominantly in the bound form, whereas in obese patients, leptin circulates mostly in the free form[12,13].

Brzechffa et al have repoted increased levels of leptin in PCOS, while others report normal leptin levels. In these studies, significant positive correlations are found between leptin levels and BMI[14].

It had also been shown that weight reduction leads to decreased serum leptin levels(15), and although BMI has been clearly shown to

be an important determinant of serum leptin milieu, other factors have also been implicated, for example estrogen has been said to be responsible for higher leptin levels in women than in men[16].

There is an increased incidence of metabolic syndrome in women with PCOS, and weight reduction is an important part of management of PCOS [17].

Insulin sensitizing drugs like metformin increase the effectiveness of insulin at the peripheral cell level and results in a decline of insulin, leading to significant improvement of clinical manifestations of hyperandrogenism[18].

In the present study leptin levels are evaluated in PCOS women before and after 3 months of metformin 500mg thrice daily looking for the enhancement of ovulation, in addition to studying the effect on other parameters including hormones, BMI,FBG and glycated hemoglobin(A1c).

Methods

Thirty six(36) patients with proven PCOS(presence of multiple ovarian cysts on ultrasound exam.with hyperandrogenemia) were included in this study which was conducted in the Specialized Center for Endocrinology and Diabetes, Baghdad, from Feb. to December 2011.Patients consent was taken, and the study was approved by the ethical comity. Their ages ranged from 17 to 36, twenty of them married and 16 were single.All of them were anovular at the time of enrolling them in the study as evidenced by u/s performed at day 12 and serum progesterone levels day 21 of the menstrual cycle . None of them has any other endocrine problem and they were on no medications before the study. Also none of them has any systemic disease.

Investigations performed on them included fasting blood glucose(FBG), glycated hemoglobin(A1c), estimation of insulin, leptin, testosterone and progesterone levels in addition to ultrasonography.Leptin , insulin and testosterone were evaluated in a fasting state regardless the state of menstruation, while progesterone was tested at day 21 of the cycle.

Treatment with metformin 500mg thrice daily was started in the and continued for 3 months.They were followed up monthly for follicular monitoring by US examination.Body mass index(BMI) was ‘measured before and after finishing the treatment.

The same investigations were repeated after 3 months of starting treatment, using the ELIZA technique for hormones.

Paired t-test was employed for statistical analysis of the parameters within the group at baseline and after 3 months of treatment.Chi square test was employed to look for statistical significance of ovulation.Statistical analysis was performed using SPSS version 10.0 statistical software. The value of $p< 0.05$ was considered significant.

Results

Metformin therapy was effective and beneficial for women after 3 months of therapy(table 1).Body mass index(BMI) was reduced($p<0.001$), mean FBG and A1c showed a significant reduction ($p<0.001$). Also there were significant reductions in the levels of insulin, leptin($p<0.001$), and a significant reduction in testosterone levels($p<0.01$) while progesterone showed a significant increase($p< 0.001$).

Ovulation was achieved in 28 women (77.78%)($p<0.01$).The mean leptin levels were reduced from 10.9±1.9 to 6.8±0.7 ng/ml($p<0.001$) in those who showed ovulation, while there was a no-significant reduction in leptin levels in those who remained anovulatory ($p>0.05$) and with mean leptin levels reduced from 7.6± 0.1 to 6.9±0.2 ng/ml.

So, ovulation was achieved only in women with significant reduction in leptin levels(table 2).

Discussion

As shown in this study all parameters were reduced after metformin therapy including BMI, FGB, A1c, insulin, leptin,and testosterone, while there was a significant increase in progesterone levels in the ovulating 28 women($p<0.001$). Also, the leptin levels in these women showed a significant reduction($p<0.001$) when compaired to the remaining still anovulatory 8 women , indicating that reducing leptin levels in PCOS women enhances ovulation. This had been observed by other investigators, who had about 93% of their

patients showing ovulation after 2 months of metformin therapy (19).

It had been said that leptin concentration is closely related to body fat mass,but still the reduction in leptin levels can not be fully explained by reduction in BMI, because metformin was found to reduce leptin levels even in normal weight healthy individuals(20).

In the present study there is a strong association between leptin and ovulation rate(table 2).Another study showed that leptin induces follicular development in ob/ob mice(ob gene means obesity gene responsible for leptin production) and formation of corpora lutea and ovulation in hypogonadal mice(21).

Another study showed that rats subjected to severe food restriction had reduced ovulation and serum progesterone, and leptin administration to these rats had enhanced ovulation(22).

A significant decrease in leptin levels is associated with a decrease in androgen concentration, hence an increase in ovulation rate(23).

As we can see in table(1) there is a significant reduction in both testosterone and leptin levels in the sera of patients enrolled in this study.

Several studies have been performed to analyse the molecular mechanisms behind th effect of metformin on leptin levels.An in vitro study reports that metformin inhibits leptin secretion in adipocytes(24).

Considering the hypothesis that PCOS is characterized by leptin resistance, a study showed that metformin restores leptin sensitivity in obese rats with leptin resistance and metformin treatment increased CSF leptin concentrations in both standard chow and high-fat-fed obese rats compaired with the untreated rats(25).

It is suggested that the increase in CSF leptin level may be the cause of reduced resistance because the defect in leptin transport through the blood-brain barrier is a possible mechanism of leptin resistance(26, 27).

Conclusion:

We concluded that metformin can reduce leptin resistance and enhance ovulation in PCOS women and may be of value in the treatment of PCOS.Metformin also reduces BMI ,blood glucose, A1c, insulin, testosterone levels while it increase progesterone levels in PCOS women.We recommend to broaden the study with metformin on a larger number of PCOS women.

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Table 1: Comparison of biochemicaland hormonal data in addition to BMI in PCOS women

Parameter	**(Mean±SE)**		**P-value**
	baseline	after3months	
BMI(kg/m^2	27.3±2	25.5±0.8	<0.001
FBG(mg/dl)	106±3	95±2	<0.001
HbA1c(%)	6.1±0.4	5.6±0.3	<0.001
Insulin(µIU/ml)	24±1.6	16.6±1.2	<0.001
Leptin(ng/ml)	10.2±1.7	6.9±0.8	<0/001
Testos.(pg/ml)	1.8±0.3	0.8±0.2	<0.01
prog.(ng/ml)	1.0±0.2	5.5±0.7	<0.001
Ovulation present	0	28	<0.01

Table 2: Comparison of serum leptin levels and ovulation

Parameter	**Mean±SE(n=28)**		**Mean±SE(n=8)**	
	baseline	after3months	baseline	after3m
Leptin(ng/ml)	10.9±1.9	6.8±0.7	7.6±0.1	6.9±0.2
	(p<0.001)		(p>0.05)	
Ovulation	absent	present	absent	absent
	(p<0.01)			

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