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Serum Adiponectin in women with polycystic ovary syndrome of different body mass index

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Abstract
Background: Polycystic ovary syndrome is an extremely common disorder in women of the reproductive age that is associated with a disturbance of reproductive, endocrine, and metabolic functions. The pathophysiology of PCOS appears to be multifactorial and polygenic. Adiponectin seems to play an important role in the pathogenesis of PCOS, especially in obese women.
Objectives: To (1) measure serum adiponectin levels in women with PCOS of different body mass index; and (2) assess possible relation between adiponectin level and the hormonal changes of the disease.
Setting: Baghdad Teaching Hospital. Duration of study one year from 2018 to 2019.
Methods: 80 women were included in this study, 40 women were suffering from PCOS (study group), and the remainder 40 were healthy women served as a control group. BMI is calculated, then each group subdivided into 2 groups: overweight with BMI$\geq$25Kg/m2 and the normal weight with BMI<25Kg/m2.
Hormonal profile: [LH, FSH, LH/FSH ratio, testosterone, TSH, T4, and prolactin] were measured. Pelvic U/S scan done to confirm the diagnosis. Serum adiponectin level was measured in both groups by Enzyme-linked immunosorbent assay [ELISA test].
Results: Mean serum adiponectin level was significantly lower in PCOS women with BMI<25Kg/m² compared to control women with BMI<25Kg/m² (17.26 ± 5.10, 26.26 ± 7.36 respectively with P-value =0.0001[<0.05]), while the mean serum adiponectin level in PCOS women with BMI$\geq$25Kg/m² was lower than control women with BMI$\geq$25Kg/m² (9.77 ± 2.01, 10.08 ± 2.70 respectively with P-value = 0.682) which is statistically not significant.
Conclusion: Adiponectin is significantly low in women suffering from PCOS.

Keywords: Erum Adiponectin, Omen With Polycystic

Introduction

Polycystic ovary syndrome
Definition: Is a common endocrine disorder affecting women of Reproductive Age. Stein and Leventhal first described the syndrome in 1935 and since then our understanding of the spectrum of disorder involved in this condition has evolved dramatically.

It is a heterogeneous collection of signs and symptoms that gathered together form a spectrum of a disorder with a mild presentation in some, while in others a severe disturbance of reproductive, endocrine, and metabolic function [1].

ESHRE/ASRM (European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine) consensus meeting is found the definition of PCOS was agreed namely the presence of two of the following criteria:

1. Oligo and/or anovulation. 2. Hyperandrogenism [clinical and/or biochemical]. 3. Polycystic ovaries [The Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group, 2004] other etiologies of hyperandrogenism and menstrual cycle disturbance should be excluded by appropriate investigations [1, 2].

Prevalence and racial differences: PCOS is thought to occur in about 6-8% of women worldwide, making it the most common reproductive disorder. However, when applying the new Rotterdam/ESHRE criteria, the prevalence is likely even higher. The prevalence is also higher in certain ethnic groups such as South Asians, who may also suffer from more severe symptoms [2].

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The highest reported prevalence of PCOS has been 52% among South Asian immigrants in Britain, of whom 49.1% had menstrual irregularity [3]. Those women appear to express symptoms at an earlier age than their Caucasian British counterparts [4].

Genetics: The PCOS has long been noted to have a familial component [5].
Genetic analysis has been hampered by the lack of a universal definition for PCOS.
Family studies have revealed that about 50% of 1st-degree relatives have PCOS suggesting a dominant mode of inheritance. Commonly 1st-degree male relatives appear more likely to have premature baldness and metabolic syndrome [1, 6].
Some studies have found an abnormality with the cholesterol side-chain cleavage gene (CYP11a), which is the rate-limiting step in steroid genesis It has been hypothesized that polymorphisms in the insulin receptor (INSR)gene that induce mild changes in insulin receptor function may contribute to the development of PCOS [1, 3].

Pathophysiology of PCOS: The exact pathophysiology of PCOS and its initiating event have yet to be elucidated However, various biochemical abnormalities have been described, and associations.
Linkages of one to another have been established. Many of these abnormalities reinforce each other in vicious circles.

Hypothalamic-pituitary abnormalities
1. Elevated LH, low-normal FSH: In PCOS, the normal pulsatile secretion of luteinizing hormone (LH) is increased by an increased frequency and amplitude of pulses while that of follicle-stimulating hormone (FSH) is unchanged or muted. Thus, LH values may be elevated, and the LH: FSH ratio can be increased to more than 2.5, even in ovulatory cycles. On the other hand, these values may be normal in as many as 10% to 20% of women with PCOS [7].

2. Elevated GnRH: The inappropriate secretion of gonadotropins is thought to be due to an abnormality of the gonadotropin-releasing hormone (GnRH) pulse generator in the hypothalamus.
It remains unclear whether this is a primary abnormality or a secondary one:
A. Evidence that it is a primary defect: comes from studies in young girls with a family history of PCOS who were entering puberty. Instead of the typical LH culpability at night seen in early puberty, LH pulses in these young girls started in the late afternoon. This indicates that the GnRH pulse generator is disrupted in very early reproductive life [8].
B. Evidence that the abnormality in the GnRH pulse generator is secondary: women develop a PCOS-like condition if they have Cushing syndrome, are exposed to anabolic steroids, or have androgen-producing tumors.
Correcting the primary abnormalities usually reverses the condition. However, there is no evidence linking hyperinsulinemia or insulin resistance to the development of a GnRH pulse generator abnormality [8, 9].

3. Elevated prolactin: Prolactin levels are elevated in about 25% of patients with PCOS.

Extreme elevations of prolactin may stimulate the adrenal production of dehydroepiandrosterone sulfate (DHEA-S). All patients with PCOS have an increased sensitivity to androgens up to:
** 70% has elevated androgen levels.
** 30% is in the high-normal range [9].

Ovarian abnormalities
1. Androstenedione: Is produced by the ovarian stromal and the cal cells in response to LH. It is normally converted to estradiol by an FSH- dependent aromatase.
Excess androstenedione in the circulation is converted to stone, which exerts a tonic effect on LH production while contributing to a relative suppression of FSH production in the face of a high LH: FSH ratio, as in PCOS, more androstenedione is synthesized but is not aromatized, thus perpetuating a vicious cycle driving LH production and some prolactin production [10].
2. Testosterone: The ovary converts some androstenedione to testosterone, and in PCOS this is amplified. Circulating testosterone comes from the ovaries and peripheral conversion.
3. Abnormalities of estrogen: Estrogen secretion is usually abnormal in PCOS, Estradiol levels may be low to normal and in the anovulatory cycle, there is tonic production without the increase before ovulation or in the mid-luteal phase as in normal women. Estrone levels increase due to extra glandular conversion of androstenedione in adipose tissue, which further stimulates LH and inhibits FSH secretion, causing stimulation and hyperplasia of the ovarian stroma and theca cells, leading to increased androgens This provides more substrate for extra glandular aromatization of androgens to estrogens and perpetuates the cycle [10, 11].
Adrenal abnormalities: Excess adrenal androgen generated during stress or adolescence or due to congenital adrenal hyperplasia because of enzyme defects might initiate the cycle of abnormal LH/FSH stimulation and lead to PCOS. DHEA-S: Pituitary gonadotropin does not directly stimulate adrenal androgens, but prolactin can stimulate DHEA-S. In the adrenal glands, DHEA-S is co-secreted with cortisol. Thus, most excess cortisol secretion as in stress or adolescence is accompanied by an elevation of DHEA-S secretion, even in the face of normal corticotrophin secretion.
At the same time, elevated levels of prolactin, seen in as many as 25% of patients with PCOS, also enhance DHEA-S secretion. While DHEA-S has little androgenic activity, small amounts can be converted to androstenedione and subsequently to testosterone [12].
Peripheral abnormalities: 1. Decreased SHBG Elevated levels of androgens in the circulation, especially testosterone, inhibit the production of hepatic sex hormone-binding globulin (SHBG). With less SHBG in circulation, more androgens are left free or unbound and therefore produce a greater clinical response in terms of hirsutus, acne, and other manifestations of androgen excess. Thus, hyperandrogenism begets more hyperandrogenism and amplifies the action [13].

2. Insulin resistance and hyperinsulinemia: Insulin resistance is present in a large percentage of women with PCOS, especially if obese, irrespective of ethnicity. Because hyperandrogenism and hyperinsulinemia coexist in PCOS, the important question is whether one causes the other.

There is no question that exogenous or tumorous hyperandrogenism can result in glucose intolerance and elevated insulin levels [12, 13]. Lowering such hyperandrogenism improves insulin resistance and acanthosis. Numerous mechanisms might explain such a link [14, 15]. However, the data for hyperandrogenism causing hyperinsulinemia are not conclusive. Numerous reports show that lowering androgen levels or attenuating their effects do not reduce hyperinsulinemia in women with PCOS. Conversely, induced hyperandrogenism in women without PCOS or in animal models does not alter insulin sensitivity. Furthermore, the insulin resistance does not seem to be due to hyperandrogenism, since it persists after oophorectomy or after ovarian androgen synthesis is suppressed by GnRH agonists [16]. Abundant evidence indicates that hyperinsulinemia begets hyperandrogenism [17].

Giving insulin to women with PCOS increases their circulating androgen levels, and lowering insulin by the administration of Diaz oxide lowers their androgen levels [18].

Furthermore, insulin sensitizers such as metformin and thiazolidinediones have been shown to reduce androgen levels and facilitate follicular maturation, normal menses, and pregnancy [19].

In vitro, insulin has been shown to stimulate androgen production in the cal cells of women with PCOS, but not in normal women. Furthermore, insulin amplifies the LH response of granulose cells, thereby causing an abnormal differentiation of these cells, the premature arrest of follicular growth, and, so, anovulation [20]. While PCOS is associated with insulin resistance and hyperinsulinemia, the ovary itself is not insulin-resistant and, in fact, possibly responds excessively to the hyperinsulinemia. Cell surface insulin receptors are at normal levels, but there is a post-receptor defect in signal transduction, causing a decrease in glucose transport. Although PCOS can be familial, genetic studies have failed to reveal any specific gene markers or chromosomal abnormalities associated with the disorder. Insulin may increase androgen synthesis by various mechanisms. It may directly increase ovarian androgen synthesis by interacting with its receptor or with the receptor for insulin-like growth factor-1. It may not only cause or worsen the altered LH secretion seen in PCOS but may change the ovarian response to LH, as described above. It also suppresses the hepatic production of SHBG, which increases free testosterone levels. Thus, insulin alters normal folliculogenesis by increasing intraovarian androgens, by altering gonadotropin release, or by direct effects on the ovary [20, 21].

Patients and Method
Study Design: Prospective Case-Control study.
Setting: Department of Obstetrics and Gynaecology/ Baghdad teaching hospital-medical city. The study protocol was approved by the Obstetrics and Gynaecology committee of the Iraqi Board for medical specialization and the hospital administration.
Patient selection: The study includes 80 women aged 14-35years (40 women with PCOS and the others 40 healthy control women) were attended the outpatient gynecology clinic of the hospital during the period from January 2011 to January 2012).

The diagnosis of PCOS was made according to (2004 the Rotterdam European Society for human reproduction /American Society for Reproductive Medicine (ESHRE /ASRM) a consensus workshop group that was held in Rotterdam, by the presence of two of the following criteria:
1. Oligoovulation or anovulation.
2. Clinical or/and biochemical signs of hyperandrogenism.
3. Polycystic ovaries.

Depending on the Gallwey score, features of hyperandrogenism clinically-based considering score 8-16 as mild hirsutus. Acne and menstrual irregularity ranged from oligo-menorrhea to secondary amenorrhea were considered also. The control group represents women with a regular cycle, no clinical features of hyperandrogenism, and no ultrasonography finding of PCOS.
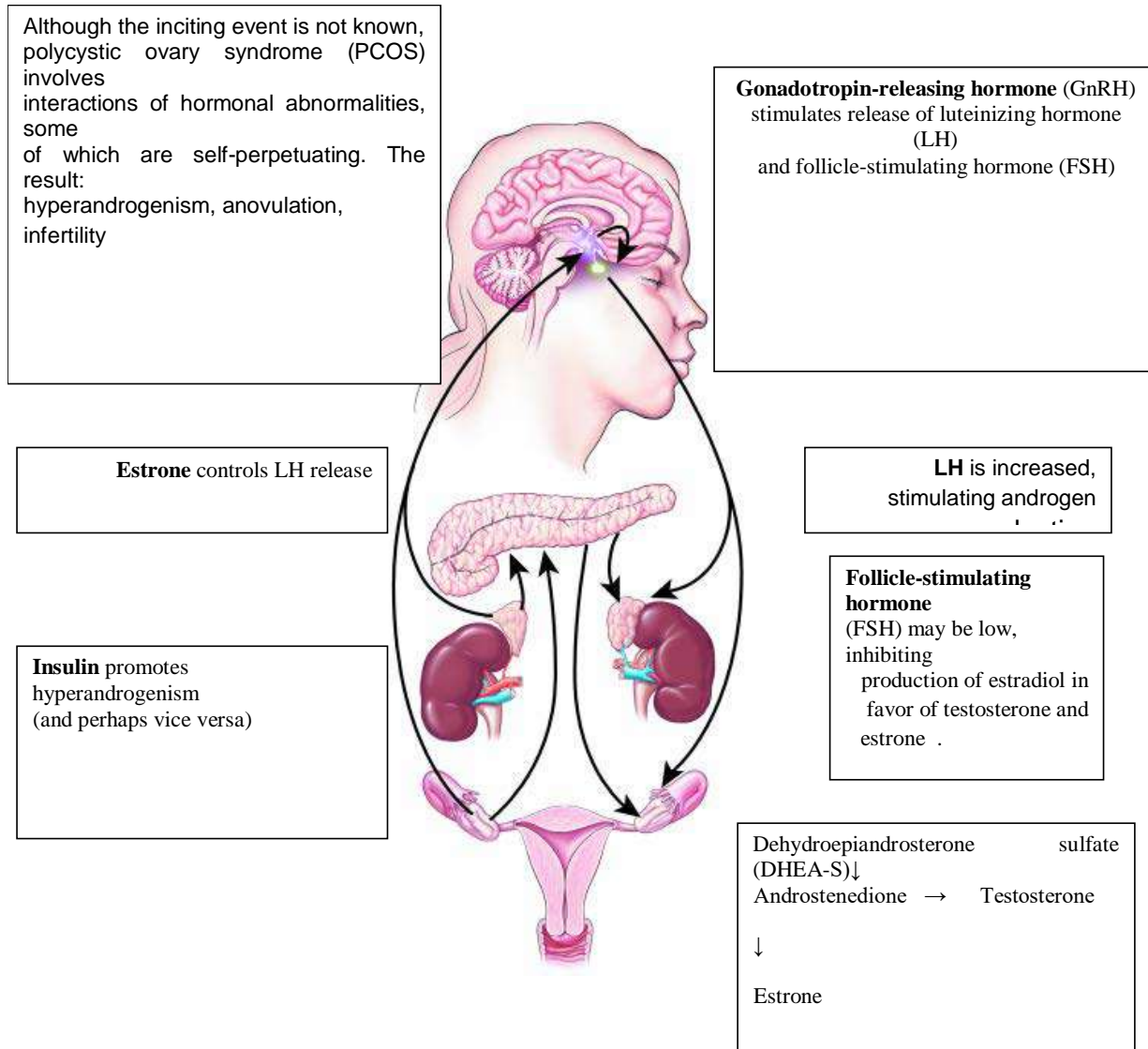
Exclusion criteria for the study groups
1. Women with Thyroid dysfunction.
2. Women with Prolactin dysfunction.
3. Women on medications, hormonal treatment, or ant obesity drugs (within 6 months) that might interfere with the normal hypothalamic-pituitary-gonadal function.
4. Women with Cushing syndrome.
5. Women with civilizing ovarian or adrenal tumor.
6. Women with congenital adrenal hyperplasia.
7. Smokers.

In both groups, full history taking and thorough examination were done and investigations were sent include measurement of the random blood sugar and the hormonal parameters: LH, FSH, prolactin, testosterone, thyroid function test, and serum adiponectin. Serum adiponectin was compared between the patients and control and also between those with BMI≥25kg/m² and those with BMI<25kg/m² subgroups. Bodyweight was measured carefully by the same balance and the patient with light clothes and without shoes, BMI was calculated for all using the following formula: {BMI=body weight (kg)/ [height (m)]²}. According to the BMI, patients, and control were sub grouped as overweight [BMI≥25kg/m²] and normal weight [BMI<25kg/m²]. Out of 40 patients with PCOS and 40 control women, 20 were normal weight and 20 were overweight.

Laboratory Measurements: Venous blood samples were taken in the early follicular phase of the menstrual cycle [day 2-6] in eumenorrheic, oligo-amenorrheic women, or at random in amenorrhea ones for LH, FSH, prolactin, TSH, T4, testosterone, and RBS that measured by standard radioimmunoassay.

Samples were taken for Adiponectin; those samples were left to stand at room temperature for about 30 minutes to allow blood to clot and then centrifuged for 10 minutes then freezing at -20°C and kept without thawing till the day of testing serum adiponectin by using ELISA sandwich kits.

Kits for the quantitative determination of human adiponectin DEMEDITEC ELISA DEE0099 (Germany) Serum level of adiponectin was quantitatively determined using a sandwich ELISA test using commercially available kits.

Although the inciting event is not known, polycystic ovary syndrome (PCOS) involves
interactions of hormonal abnormalities, some
of which are self-perpetuating. The result:
hyperandrogenism, anovulation, infertility

Gonadotropin-releasing hormone (GnRH) stimulates release of luteinizing hormone (LH)
and follicle-stimulating hormone (FSH)

Estrone controls LH release

LH is increased, stimulating androgen

Follicle-stimulating hormone
(FSH) may be low, inhibiting
production of estradiol in favor of testosterone and estrone .

Insulin promotes hyperandrogenism
(and perhaps vice versa)

Dehydroepiandrosterone   sulfate
(DHEA-S)↓
Androstenedione   →   Testosterone

↓

Estrone

Fig 1-1: Pathophysiology of PCOS [9]

Statistical analysis: Analysis of data was carried out using the available statistical package of SPSS-20 (Statistical Packages for Social Sciences- version 20).

Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of the difference of different means (quantitative data) was tested using an independent student-test for the difference between two means, while different percentages (qualitative data) were tested using the chi-square test (χ^2-test). Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) either positive (direct correlation) or negative (inverse correlation) with value <0.3 represent no correlation, 0.3-<0.5 represent weak correlation 0.5-<0.7 moderate strength ≥0.7 strong correlation. Statistical significance was considered whenever the P-value was equal or less than 0.05.

Discussion

Polycystic ovary syndrome is a heterogeneous condition. The diagnostic criteria are clear including menstrual disorders, clinical or biochemical features of hyperandrogenism, and the characteristic ultrasound picture of ovaries. There are several other problems, mainly endocrinology and metabolic ones, including obesity which also belongs to the clinical picture of the disease [1].

Adiponectin is probably one of the most important adipocytokines of the adipose tissue. It is highly expressed and actively secreted by adipocytes, it is abundantly present in the human circulation and displays a variety of functions, including antiatherogenic, anti-inflammatory, and insulin-sensitizing properties [51, 52].

In our study, all women were carefully selected regarding weight, height, and BMI, Adiponectin was significantly lower in women with PCOS when compared to control, P-value of 0.011(<0.05), because in our study we divided the PCOS and control, women, into subgroups according to their BMI, we found that Adiponectin significantly low in PCOS women of normal weight, in comparison with control women of normal weight, with a P-value of 0.0001.

Conclusion and Recommendations

Conclusion: Adiponectin is significantly low in women suffering from PCOS.

Recommendations

1. Further studies for a longer duration with a larger sample size are needed to determine a clear relationship

between adiponectin level and other causes involved in the pathogenesis of PCOS.

2. Further investigation is required to prove whether these findings may be of clinical significance in the management of patients with PCOS, especially in the diagnosis of PCOS in lean bodyweight women or the avoidance of over diagnosis of PCOS in obese women and may be of clinical significance in the management of infertility.

3. We recommended that all women who have BMI≥25Kg/m² to decrease the weight to increase adiponectin level in their blood to control abnormal hormonal secretion.

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