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Effect of Obesity on Some of Metabolic Hormones and Proinflammatory Cytokines in Patients with Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility, it is identified as hyperandrogenism, chronic anovulation and metabolic disorder. The current study aimed to evaluate the effect of obesity on some of metabolic hormones and proinflammatory in patients with PCOS compared with control group. This study includes 150 women , were divided in to 75 healthy fertile women as control group and 75 women diagnosis with PCOS. Each group was divided into four categories depending on BMI (normal, pre-obesity, obese class I and obese class II). Then the concentrations of the study parameters were measured by using ELIZA method. The results revealed that PCOS patients with pre- obesity BMI had effect on the levels of all parameters expect T4 compared with control group ,while PCOS patients those belong to the obese class1 category showed a significant differences in TSH,T3,T4 only, and obese class II category showed a significant differences in T3, insulin and cortisol. TNF-α levels in per-obesity categories are significant and IL-18 concentration in per-obesity , obese class I and class II are significant In. In conclusions obesity my induce abnormalities in metabolic hormones and proinflammatory cytokines in PCOS patients.

Keywords

polycystic ovary syndrome, PCOS , IL-18, TNF- α.

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1-Introduction

Polycystic Ovary Syndrome (PCOS) was defined not only as a gynecologic endocrinopathy, but also as a kind of metabolic disorder [1] . patients with PCOS have an increased risk of complications that related to pregnancy such as preeclampsia and gestational diabetes mellitus, also pregnancy induced hypertension, premature delivery and caesarean section [2] . PCOS patients have extravagant fat in the visceral deposits, which it plays a crucial role in cardiovascular disease, this altered fat distribution is present in both obese PCOS women and normal weight PCOS women, these adipocyte dysfunction and chronic low grade inflammation could be a novel mechanisms involved in cardiovascular disease in PCOS [3] . many PCOS women have abdominal obesity which leads to adipose tissue dysfunction, characterized by hypertrophic adipocytes, lipolysis impairments and insulin action, the secretion and expression of adipokines involved in insulin resistance such as adiponectin hormone and dysfunction in the adipose tissue plays an important role in the metabolic abnormalities in PCOS [4] . Obesity has effects on both clinical manifestation and pathophysiology of PCOS compared with normal weight PCOS women, these women with obesity have the worst hyperandrogenic and metabolic state, ovulatory rendering, poorer menses and pregnancy rates, obesity is not only an effect on metabolic modulation hyperandrogenism but also on ovulation and fertility [5] . PCOS causes entanglements for pregnancy outcomes and long term health of these women and their offspring. Whether PCOS itself or it's symptoms such as obesity and infertility are responsible for these implications is unknown, miscarriage rates among PCOS women are increased compared with women that influenced by weight, PCOS women showed an increased risk of neonatal complications such as acceptance at a neonatal intensive care unit and preterm birth [6] .PCOS is characterized by menstrual irregularity, hyperandrogenism, it is also linked to several long term health risks such as central obesity, dyslipidemia, insulin resistance, type 2 diabetes, hyperinsulinemia, hypertension, cardiovascular diseases and higher rate of early loss of pregnancy [7]. Under the effect of genetics, obesity and life style factors, two abnormalities would develop: First, the insulin resistance which leads to hyperinsulinemia. Second, increased GnRH pulsatile release which leads to increased LH:FSH ratio. These abnormalities cause androgen excess; as a result the high levels of androgen cause arrest in antral follicle development forming PCO and anovulation (no corpus luteum), leading to a decrease in progesterone ,estrogen levels and irregular cycles [8]. there is a confusion in biochemical and hormonal condition of PCOS women which leads to endocrinological surge and a changed energy metabolism in PCOS. both abdominal obesity and hyperandrogenism contribute to dyslipidemia and other metabolic characters of PCOS [9].

2-Methods

Current study included 75 PCOS patient group and 75 and healthy women as control both groups are divided into four categories according to their BMI (normal, pre-obesity, obese class I and obese class II), the blood collection was performed during the luteal phase of the menstrual cycle. 10 ml of venues blood samples were collected in Gel/clot activator tubes and serum was separated by using centrifuge (3500 rpm-10minutes), the serum divided in to eppendorf tubes and kept frozen at (-20 C°) with avoiding multiple freezing. The analysis includes the using of ELIZA method kits for measuring of TSH (Bioactiva diagnostic, Germany), T3 and T4 Insulin (Monobind Inc, USA) kits, cortisol (Human, Germany) kit, Serum IL-18 (Al-shkairate/ Jordon) and TNF-α (Diclone/ France) . The procedure of kits followed as established in the kits leaflet.

The statistical analysis:

The statistical analysis are performed by using SPSS version 20 with $P<0.05$, $P\leq0.01$at a significant, Data are expressed according to Mann-Whitney Test, multivariate Anova and Kruskal-Wallis Test.

Estimation of Body Mass Index (BMI):

BMI for both PCOS patient and control women was measured as following : weight (kilogram)/ hight2 (meter 2) .The BMI definition that established by WHO, which is the most common used (Normal; 18.5-24.9/ Pre-obesity ; 25.0-29.9/ Obese class I/ 30.0–34.9, Obese ≥ classII; 35.0-39.9/ Obese class III; 40).

3-Results

Kruskal-Wallis test showed that all metabolic hormones are significant between all BMI categories of control group and PCOS patients, except T4 is not significant. As shown in the tables (1,2), normal BMI and pre-obesity categories showed a significant ($P\leq0.05$) increase in the level of TSH, T3, cortisol and insulin levels in PCOS patients compared with control group and, while T4 is not significant. Obese class I categories showed a significant ($P\leq0.05$) increase in the levels of insulin and cortisol in PCOS patients compared with control group, while TSH ,T4 ,T3 are not significant, table(3). Obese class II category showed a significant ($P\leq0.05$) increase in the level of T3, cortisol and insulin in PCOS patients compared with control group, while TSH and T4 are not significant between two groups, table (4) . The comparison between BMI categories of PCOS patients showed no significant variance in the level of metabolic hormones between PCOS BMI categories.

Table 1- Comparison of metabolic hormones between control group and PCOS patients according to normal BMI category. Values was expressed as (median (min- max)).

BMI	**Normal (18.5-24.9 kg/m2) (n=46)**	**Normal (18.5-24.9 kg/m2) (n=17)**
TSH (µU/ml)	1.18 (0.12-3.70)	1.05 (0.34-5.11)**
T3 (µg/dl)	0.95 (0.52-1.92)	1.30 (0.82-1.87)*
T4 (µg/dl)	7.70(4.51-11.90)	8.68(3.82-13-94)
Insulin(µU/ml)	4.99 (0.79-109.11)	62.76 (3.15-145.31)**
cortisol(ng/ml)	93.90(56.19-250.01)	213.19(21.08-413.63)*
*Significant at the (P≤0.05) ** significant at the (P≤0.01)		

Table 2- Comparison of metabolic hormones between control group and PCOS patients according to pre-obesity BMI category. Values was expressed as (median (min- max)).

BMI	**Pre-obesity (25.0-29.9 kg/m2) (n=20)**	**Pre-obesity (25.0-29.9 kg/m2) (n=23)**
TSH (µU/ml)	0.85 (0.32-3.25)	1.70 (0.74-17.02)**
T3 (µg/dl)	0.71 (0.13-1.80)	1.38 (0.74-9.34)**
T4 (µg/dl)	7.88(1.50-11.29)	7.18(1.90-13.94)
Insulin(µU/ml)	4.59 (0.74-100.31)	67.22 (3.10-194.52)**
cortisol(ng/ml)	99.70 (55.01-250)	271.01 (40.85-577.36)**
*Significant at the (P≤0.05) ** significant at the (P≤0.01)		

Table(3): Comparison of metabolic hormones between control group and PCOS patients according to obese class 1 BMI category. Values was expressed as (median (min- max)).

BMI	**Obese class I (30.0–34.9 kg/m2) (n=6)**	**Obese class I (30.0–34.9 kg/m2) (n=24)**
TSH (µU/ml)	0.75 (0.43-3.05)	1.72 (0.40-5.31)
T3 (µg/dl)	1.50 (0.81-1.93)	1.35(0.36-2.04)
T4 (µg/dl)	7.55(5.41-11.71)	8.09(1.57-14.21)
Insulin(µU/ml)	3.86 (1.31-8.63)	62.97(1.90-196.07)**
cortisol(ng/ml)	89.910(59.34-195.20)	226.90(17.45-670.14)*
*Significant at the (P≤0.05) ** significant at the (P≤0.01)		

Table 4- Comparison of metabolic hormones between control group and PCOS patients according to obese class II BMI category. Values was expressed as (median(min-max).

BMI	**Obese class II (35.0-39.9 kg/m2) (n=3)**	**Obese class II (35.0-39.9 kg/m2) (n=11)**
TSH (µU/ml)	0.70 (0.70-0.83)	1.83 (0.49-0.70)
T3 (µg/dl)	1.00 (0.71-1.83)	1.02 (0.45-1.89)**
T4 (µg/dl)	10.71 (9.02-11.56)	7.07(1.61-19.77)
Insulin(µU/ml)	3.50 (3.02-7.88)	35.27 (2.49-130.93)*
cortisol(ng/ml)	125.25 (62.20-172.19)	211.87(68.07-642.51)*
*Significant at the (P≤0.05) ** significant at the (P≤0.01)		

Kruskal-Wallis test showed that serum TNF-α and IL-18 levels are significant between all BMI categories of control group and PCOS women, As in the table 6), the comparison between BMI categories of control group and PCOS patients showed that TNF-α levels in normal BMI ,per-obesity categories are significant, while obese class I and class II categories are not significant. IL-18 concentration in normal BMI, per-obesity , obese class I and class II

are significant. The comparison between BMI categories of PCOS patients showed no significant variance in the level of TNF-α and IL-18 between any of PCOS BMI categories.

Table 5- Comparison of Proinflammatory Cytokines between control group and PCOS patients according to BMI categories. Values was expressed as (median (min-max)).

Proinflammatory Cytokines	**Control (n=28)**	**PCOS (n=60)**
BMI	**Normal (18.5-24.9 kg/m2)**	**Normal (18.5-24.9 kg/m2)**
TNF-α(pg/ml)	2.95 (0.2-12.08)	10.24 (0.92-20.05)**
IL-18(pg/ml)	0.72 (0.15-26.97)	44.15 (3.68-92.53)**
BMI	**Pre-obesity (25.0-29.9 kg/m2)**	**Pre-obesity (25.0-29.9 kg/m2)**
TNF-α(pg/ml)	2.47 (0.34-3.56)	14.28 (0.12-40.82)*
IL-18(pg/ml)	0.57 (0.19-6.62)	45.220(4 -122.42)**
BMI	**Obese class I (30.0–34.9 kg/m2)**	**Obese class I (30.0–34.9 kg/m2)**
TNF-α(pg/ml)	0.67(0.2-10.829)	12.76 (0.78-40.83)
IL-18(pg/ml)	0.97(0.7-5.22)	63.53 (4.89-159.24)**
Weight	**Obese class II (35.0-39.9 kg/m2)**	**Obese class II (35.0-39.9 kg/m2)**
TNF-α(pg/ml)	3.16 (0.23-6.09)	8.96 (1.87-55.67)
IL-18(pg/ml)	4.28 (2.66-5.9)	43.82 (6.32-80.64)*
*Significant at the (P≤0.05) ** significant at the (P≤0.01)		

4-Discussion

Obesity in PCOS women presents in various degrees and is associated with insulin resistance and hyperandrogenemia [10]. Elevated TSH levels were found to be related

positively with elevated cortisol and this relationship may be a sign of pathologic disorder [11]. One of the studies recorded a significant increase in prolactin and TSH in PCOS females compared with control, the degree of obesity in PCOS patients could be a key factor that influences thyroid hormones level [12]. Obesity and PCOS share many of the same metabolic disorders such as hyperinsulinemia and hyperandrogenism with subsequent insulin resistance, the metabolic disorders in adolescent PCOS are worsened by obesity. normal weight and obese PCOS adolescents had significantly low SHBG and HDL-C, significantly high TG, ,insulin, LDL-C and testosterone [13]. Excess cortisol stimulates the moving of fatty acid from the adipose tissue in to the blood, causing obesity, this obesity results from excess stimulation of food intake and these fat being made body tissues more rapidly than it is mobilizing and oxidizing, individuals with abdominal obesity have high levels of cortisol, whereas both stress and cortisol control the eating behaviors and energy spending, cortisol also increases the utilization of foods that rich with fat and sugar, and it was found that women with high cortisol have greater tendency to weight gain by more eating [14]. Insulin resistance is a common feature of PCOS women but it is not universal and different between clinical phenotypes of PCOS and obesity may contribute to the association between PCOS and insulin resistance [15]. The inability of insulin to function normally may cause PCOS**.** women have a difficulty in losing weight [16]. Hyperinsulinemia involves in hyperandrogenism by inhibition the hepatic SHBG production and stimulation the ovarian androgen secretion. Adipose tissue dysfunction also involves in the insulin resistance in PCOS patients [17]. Obesity is an important factor that influences the increased levels of insulin in serum but appeared to have an independent effect on metabolic syndrome risks [18]. [19] showed that moderately elevated testosterone and obesity that related with inflammatory factors adjust glucose homeostasis by increasing early insulin secretion and insulin resistance. TNF- found to be play a major role in the insulin resistance pathogenesis by inhibiting the tyrosin phosphorylation of insulin receptor and of insulin receptor substrate-1 in fat and muscle cells [20]. TNF-α is increases in obesity and have an effect on insulin action in some tissues. In PCOS induces an inflammatory condition worsened when obesity is present, The elevated TNF-α, could effect on glucose absorption in the tissue and may cause fertility collapse in PCOS women [21]. Meta-analysis of the 31 articles meeting inclusion criteria showed that circulating CRP was 96% higher in women with PCOS compared with controls is independent of obesity. Meta-analyses that involved 10 studies of IL-6, and nine studies of TNF-α revealed no statistically significant differences between PCOS women and controls [22]. Meta-analyses that involved 10 studies of IL-6, and nine studies of TNF-α revealed no statistically significant differences between PCOS women and controls [58]. Highly sensitive C-reactive protein (hsCRP), IL-6 and leukocyte numbers were found to be higher in PCOS patients than control and correlated with HDL-C, Body Mass Index (BMI), insulin resistance and diastolic blood pressure also BMI was a major predictor of immune markers and explained many variances. Obesity plays a vital role in inflammatory processes

linked to cardiovascular risk in PCOS patients. Even lean PCOS patients may display subtle changes in immunity [23]. Adipose tissue, particularly visceral fat might produce IL-18, clearing up the increase in serum IL-18 levels in PCOS women who have usually a visceral adiposity, genetic variability in the gene encoding IL-18 might be related to PCOS, obesity, and insulin resistance [24]. IL-18 as an indicators of inflammation in the adipose tissue and their higher levels in circulating system are revealed in PCOS obese women [25]. In conclusions the current study showed that obesity in PCOS patients worsen the metabolic hormones and inflammatory abnormalities compared with healthy women, through increasing the serum levels of TSH, T3,cortisol, insulin, IL-18 and TNF- α. Therefore, women should be directed to reduce weight to prevent the occurrence of such disorders and exacerbation of PCOS symptoms.

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