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Differential Levels of DHEAS and Inflammatory Cytokines in Obese and Non-Obese Women with Polycystic Ovary Syndrome (PCOS): A Comparative Study

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder with symptoms and diverse clinical manifestations. Obesity, a common comorbidity in PCOS, may exacerbate and lead to varied hormonal and inflammatory profiles. This study aimed to compare serum DHEAS, TNF-α, and IL-10 levels between obese and non-obese women with PCOS, providing insights into the intricate interplay between obesity, hormonal imbalances, and inflammation in this condition and offering potential pathways for enhancing fertility treatment outcomes in this challenging patient population. In this cross-sectional study, the data was analyzed from sixty -five women diagnosed with PCOS, categorized into two groups based on their Body Mass Index (BMI): Thirty-eight were non-obese (BMI < 30) and twenty-seven obese women (BMI ≥ 30). Serum samples were collected to measure DHEAS, TNF-α, and IL-10 levels using the ELIZA kit. These measures were then compared between the two groups to ascertain any significant differences.

The study found significantly higher serum DHEAS levels in non-obese PCOS patients compared to their obese counterparts (p = 0.01). However, no significant difference was observed in serum TNF-α and IL-10 levels between the two groups (TNF-α p = 0.58; IL-10 p = 0.13). Serum DHEAS were significantly higher in non-obese compared to their obese counterparts' women with PCOS. In contrast, no significant variance was found regarding S.TNF-α and S.IL-10 between the two groups

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KEYWORD

Obesity, PCOS, S. DHEAS, S.TNF-α, S.IL-10

1. Introduction

PCOS is a complex endocrine disorder that is recognized as one of the most common hormonal disturbances affecting women of reproductive age (WHO, 2023[1]). It is one of the leading causes of infertility due to its impact on ovulation, it is estimated to affect approximately 6-10% of women worldwide (Liu et al., 2021[2]). PCOS is characterized by a range of clinical manifestations, which typically include irregular menstrual cycles, hyperandrogenism, and polycystic ovaries observable through ultrasound. Additionally, the syndrome is often associated with various metabolic issues, including insulin resistance, obesity, type 2 diabetes mellitus, and cardiovascular risks, making its management a multidisciplinary concern (Legro RS, et al., 2021[3]) .

Obesity is a common comorbidity in PCOS, with studies suggesting that 40-80% of women with PCOS are overweight or obese (Barber & Franks, 2021 [4]). Obesity exacerbates the metabolic and reproductive abnormalities associated with PCOS, and there is growing evidence that it may also influence the endocrine and inflammatory environments in PCOS including DHEAS, TNF-α, and IL-10 levels (Goodarzi et al., 2015[5]) (Rudnicka et al., 2021[6]).

DHEAS is a crucial hormone produced primarily by the adrenal glands and serves as a precursor to both androgens and estrogens. Elevated levels of DHEAS have been observed in many women with PCOS and are thought to contribute to the hyperandrogenism that characterizes the disorder (Khan et al., 2021 [7]). The relationship between DHEAS levels and PCOS symptoms is complex and influenced by various factors, including obesity. However, the interaction between obesity, DHEAS levels, and PCOS remains

incompletely understood, with existing studies offering conflicting results (Goodarzi et al., 2015[5]) .

TNF-α is a pro-inflammatory cytokine involved in systemic inflammation. In PCOS, TNF-α levels have often been found to be elevated. This elevation is linked to the chronic low-grade inflammation that is commonly observed in PCOS patients (Rudnicka et al., 2021[6]). Some studies suggest that it may increase the effect of DHEAS levels (Vujovic et al., 2021[8]).

In contrast, IL-10 is an anti-inflammatory cytokine that plays a crucial role in controlling inflammatory responses (Zhai & Pang, 2022[9]). In PCOS, the levels of IL-10 are a subject of ongoing research, with some studies suggesting reduced levels of this cytokine and might contribute to the persistence of a pro-inflammatory state, as IL-10 is important in counteracting the effects of pro-inflammatory cytokines like TNF-α (Gao et al., 2016 [10]). Understanding the interplay of DHEAS, TNF-α, and IL-10 levels in women with PCOS, especially considering the impact of obesity, is crucial for developing tailored treatment approaches. This study contributes to the growing body of research on the hormonal and immunological aspects of PCOS, offering potential pathways for better fertility treatment in this interesting patient population.

2. Patients and Methods

A prospective comparative study was conducted at the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies consultation clinic, Al-Nahrain University, Baghdad, Iraq. The study spanned from December 2021 to April 2023, involving 82 sub-fertile PCOS women diagnosed with PCOS according to the Rotterdam criteria of 2003. 15 patients were excluded from this study as they declined to participate, and an additional two were

excluded due to their use of anti-inflammatory drugs, which could potentially influence the inflammatory marker levels being studied. All participants were aged between 20 and 39 years.Each couple underwent a comprehensive fertility evaluation at the fertility center, encompassing a detailed medical history and examination, monitoring of ovulation, evaluation of tubal patency and uterine cavity, and seminal fluid analysis. Assessment of the baseline fertility tests including FSH, LH, AMH, TSH, Prolactin, and basal E2 to evaluate ovarian reserve and other factors that could affect IVF success. All these are done on day 2 of the menstrual cycle. Blood samples were collected from each PCOS woman via venipuncture and then centrifuged at 3000 g for 15 minutes., The serum was separated after centrifugation and stored at -20°C for subsequent analysis to measure the concentrations of serum levels of DHEAS, TNF-α, and IL-10 using the Enzyme-Linked Immunosorbent Assay (ELISA) kits provided by YL Biont Shanghai, China .

The women involved in this study were categorized into two distinct groups based on their BMI classifications (non-obese <30 kg/m2, obese ≥ 30). BMI, or Body Mass Index, is calculated using the formula involves dividing a person's weight in kilograms by their height in meters squared:

BMI = (Height in meters)2/Weight in kilograms.

Inclusion Criteria:

The study included women within the age range of 20 to 39 years. Eligible participants were those who were diagnosed with PCOS and used a GnRH antagonist protocol for pituitary suppression during the ICSI cycle and consented to be part of the study.

Exclusion Criteria

Excluded from the study were women undergoing pituitary suppression with GnRH agonists, Individuals exhibiting any endocrine disorders or immunological diseases such as thyroid dysfunction, high prolactin levels, late-

onset congenital adrenal hyperplasia, Cushing's syndrome, or hypogonadotropic hypogonadism, as well as women aged 40 years or older.

Ethical consideration

This study was conducted adhering to the ethical principles outlined in the Declaration of Helsinki. Informed consent, both verbal and written, was obtained from each patient before sample collection. The study's protocol, participant information, and consent forms were reviewed and approved by a local Ethics Committee, ensuring compliance with ethical standards.

3. Statistical Analysis

The data gathered in this study were systematically coded and tabulated, utilizing Microsoft Excel 2019 for initial organization and analysis. Further detailed statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 23.0. The results are presented as means along with their standard deviations. For comparative analysis between the two groups, the student's paired t-test was employed. A significance level was established, with P-values less than 0.050 considered indicative of statistical significance.

4. Results

Sixty- five PCOS women with ages ranging between 20-39 participating in this comparative study were categorized into two groups based on their BMI as illustrated in Figure 1:

The first group consisted of twenty-seven obese females, representing 41.53% of the women participating in the study while the second group was composed of thirty-eight non-obese females, accounting for 58.46% of the participants in the study. As shown in Table 1, the average age of women in the non-obese group was slightly lower than that in the obese group, but the difference was not statistically significant, also the duration of infertility was comparable between the two groups. Hormonal profiles, including FSH, LH, AMH, TSH,

prolactin, and estradiol (E2) levels, also did not show significant differences between non-obese and obese groups, suggesting that these endocrine factors are not markedly influenced by BMI in this population. Table 2 and Figure 2, shows a significant difference in DHEAS Levels between non-obese (Mean ±SD=205.64± 33.42) and obese groups (Mean ±SD=182.04± 34.08) with p value= 0.01. while no significant difference between the two groups regarding S. TNF and S. IL10 as shown in Figures 3 and 4.

Table *(1):* Demographic characteristics of infertile women according to PCOS status

Characteristic	**Non -Obese (BMI <30) N=38** (Mean ±SD)	**Obese (BMI ≥ 30) N=27** (Mean ±SD)	***P value***
Age (years)	29.50± 4.88	31.11± 5.51	0.22
Duration of infertility	7.30± 3.87	8.35± 4.64	0.33
FSH	5.14± 1.29	5.81± 1.87	0.09
LH	4.94± 1.58	5.40± 2.24	0.34
AMH	3.68± 1.34	4.00± 0.98	0.30
TSH mIU/L	2.17± 0.62	2.06± 0.63	0.50
Prolactin mIU/ml	19.66± 5.01	19.89± 3.88	0.84
E2 (pg./ml)	36.78 ±8.76	36.52 ±8.33	0.69

N: *number of cases;* ***SD****: standard deviation;* ***BMI:*** *body mass index* ***FSH:*** *follicle stimulating hormone;* ***LH:*** *luteinizing hormone;* ***TSH:*** *thyroid stimulating hormone;* ***E2****: estradiol: significant at* ***P*** *<0.05.*

Table (2): Table 2: Serum Levels of DHEAS, TNF-α, and IL10 concerning BMI in PCOS Women.

parameters	**Non -Obese (BMI <30) N=38** (Mean ±SD)	**Obese (BMI ≥ 30) N=27** (Mean ±SD)	***P value***
S. DHEAS	205.64± 33.42	182.04± 34.08	0.01*
S. TNF-α	76.94± 17.98	74.68± 12.98	0.58
S. IL10	75.04± 17.58	83.10± 24.85	0.13

***n*:** number of cases; SD: standard deviation; †: Independent samples t-test; **MI**: metaphase I (immature) oocytes; **MII**: metaphase II (mature) oocytes; **PN**: pro-nuclei; **NS**: not significant at $P > 0.05$; HS: highly significant at $P \leq 0.01$

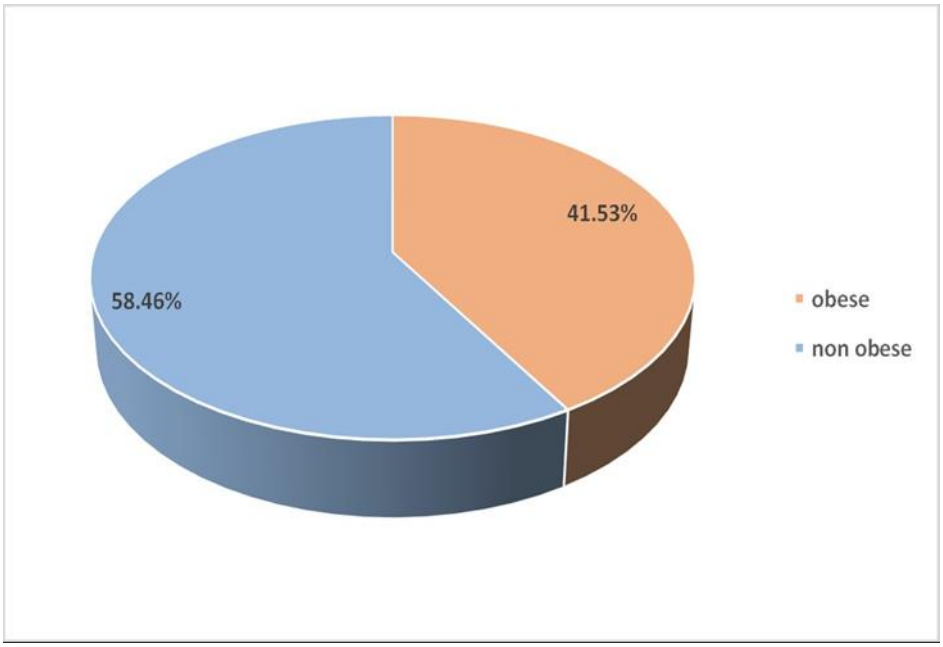

Figure (1): PCOS women were divided into two groups according to BMI.

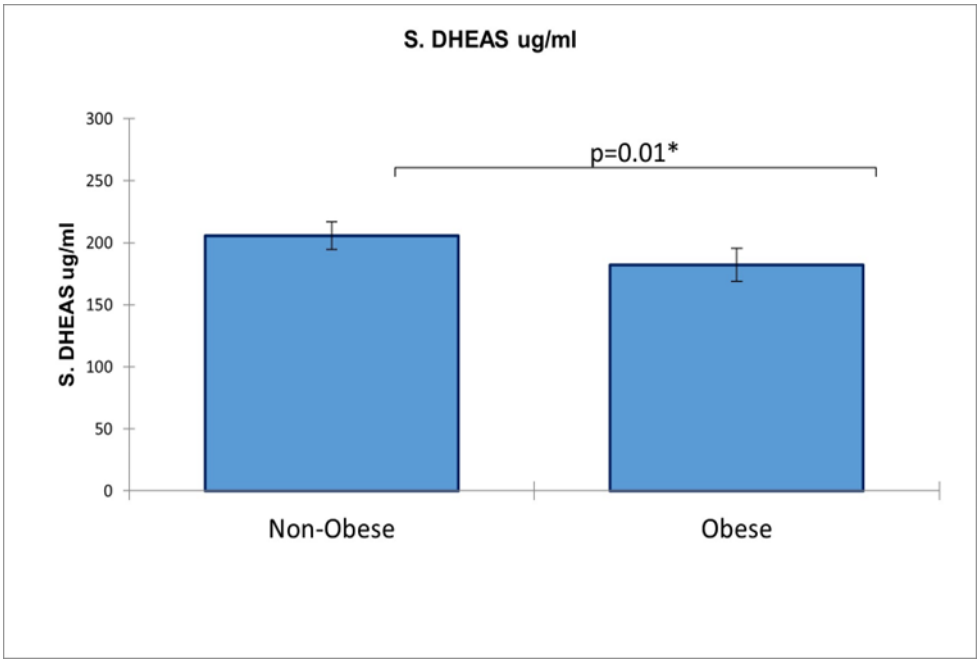

Figure (2): Comparison of Serum DHEAS Levels Between Non-Obese and Obese PCOS Women indicating Significantly Higher Levels in Non-Obese Individuals. *: significant at level $p<0.05$.

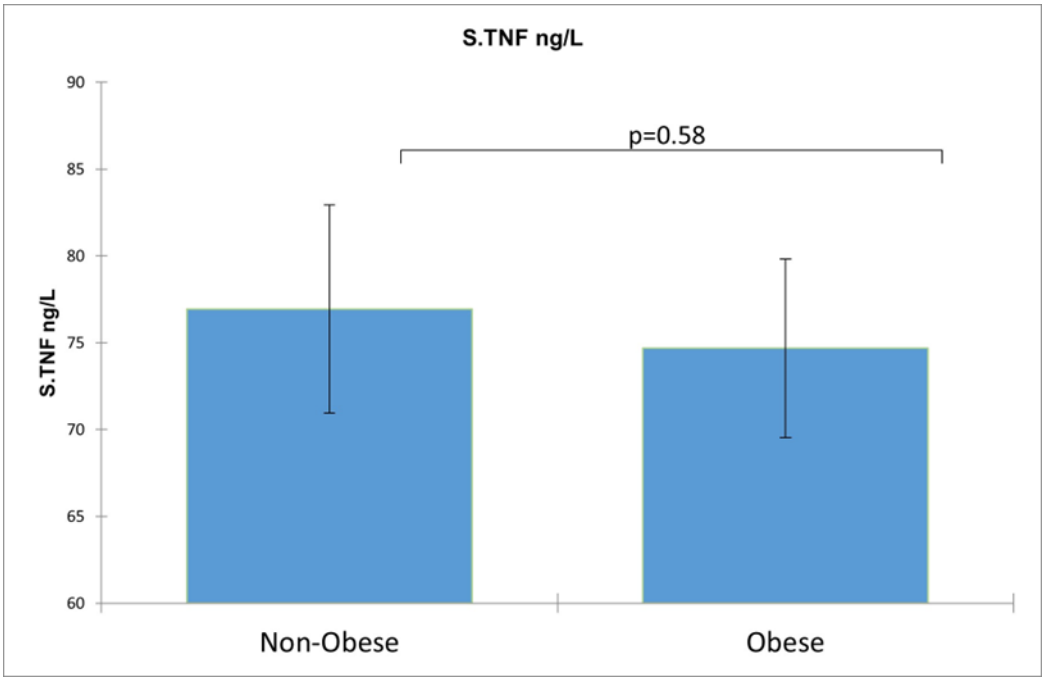

Figure (3): Serum TNF Levels in Non-Obese and Obese PCOS Women reveal no Significant Difference Indicated by Statistical Analysis. significant at P <0.05.

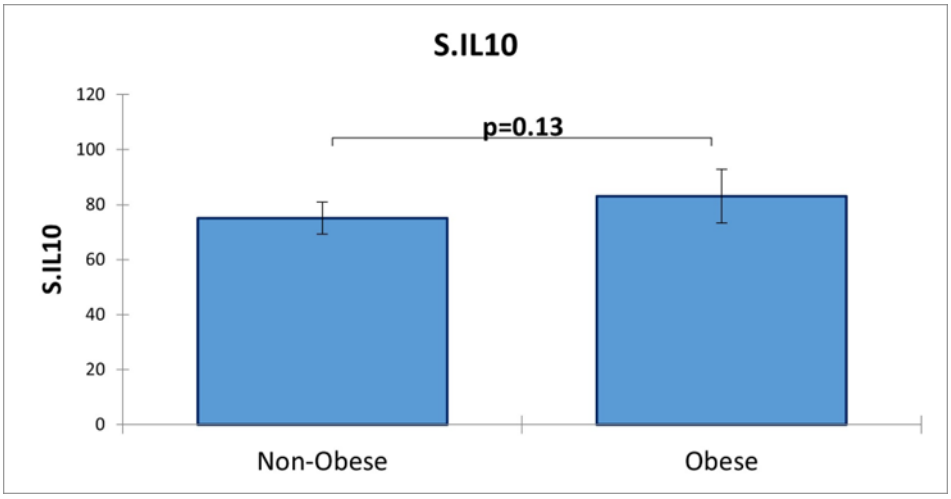

Figure (4): Serum IL10 Concentrations in Non-Obese Versus Obese Women demonstrate no significant difference between the Obese and non-obese groups. significant at P <0.05.

5. Discussion

The results of this study showed a significantly higher serum DHEAS level in the non-obese PCOS group compared to their obese counterparts. This finding concurs with the work of Khan et al. (2021), who reported heightened DHEAS levels in non-obese women with PCOS (Khan et al., 2021[7]).

This difference is remarkable as it suggests that obesity might influence androgen levels in women with PCOS. Higher DHEAS in non-obese women could be due to the lessened impact of adipose tissue on hormone metabolism (Kuryłowicz, 2023[11]). Adipose tissue plays a significant role in the metabolism of hormones, particularly sex steroids like androgens and estrogens. It expresses the aromatase enzyme, which converts androgens including DHEAS into estrogens. Aromatase activity is higher in adipose tissue, which means that individuals with higher levels of body fat are likely to convert more androgens into estrogens leading to lower DHEAS levels (Ostinelli et al., 2022[12]).

In contrast, in non-obese individuals, there is generally less adipose tissue, and consequently, potentially lower aromatase activity. This reduced conversion rate might lead to higher levels of circulating androgens, including DHEAS since less of it is being converted to estrogen. Therefore, non-obese women with PCOS might exhibit higher serum DHEAS levels due to this diminished aromatization process (Escobar-Morreale, 2018 [13]). The elevated DHEAS in non-obese women may also be reflective of a less severe endocrine phenotype of PCOS or a different subtype of the syndrome, which aligns with the heterogeneity of PCOS (Shirazi et al., 2021 [14]) .

Furthermore, the interaction between obesity, insulin resistance, and hormonal balance is complex. Insulin resistance, which is more common in obese individuals, may lead to

compensatory hyperinsulinemia. High levels of insulin can exert a suppressive effect on the adrenal gland's production of DHEAS, further contributing to lower levels of this hormone in obese individuals (Keskin Kurt et al., 2014[15]).

The study also evaluated serum TNF-α levels, a pro-inflammatory cytokine, and found no significant differences between the non-obese and obese PCOS groups. This result might indicate that the inflammatory state may be a characteristic of PCOS itself, rather than being solely exacerbated by obesity. This could indicate that the presence of PCOS, regardless of the individual's body mass index, is enough to sustain an inflammatory state, which is not significantly worsened by the addition of obesity (Vasyukova et al., 2023 [16]). This finding corresponds with research indicating elevated inflammatory markers in both lean and obese individuals with PCOS. Additionally, it is hypothesized that chronic low-grade inflammation in PCOS may have a genetic basis (Sathyapalan & Atkin, 2010 [17]). This suggests that the inflammation observed in PCOS could be inherently linked to the disorder itself, rather than being a consequence of obesity. Another explanation is that increased visceral obesity that is observed in lean PCOS women could be a cause of excess TNF-α. (Ihsan et al., 2018 [18])

In contrast, some studies suggest that obesity in PCOS exacerbates the inflammatory response, thus increasing TNF-α levels (Gao et al., 2016 [10]) (Xiao et al., 2023[19]). On the other hand, the absence of significant differences in TNF-α levels suggests that factors other than obesity might play a more predominant role in the inflammatory aspects of PCOS .

Regarding IL10, an anti-inflammatory cytokine, the study similarly found no significant differences between the non-obese and obese PCOS groups. The production of IL-10 may be upregulated in all women with PCOS

as a compensatory response to systemic inflammation, regardless of their obesity status. This response might be a regulatory mechanism aimed at controlling the pro-inflammatory state common in PCOS as it functions to suppress the activity of pro-inflammatory cytokines including TNF-α (Sathyapalan & Atkin, 2010 [17]).

In contrast, other studies hypothesized that obese individuals might have lower levels of anti-inflammatory markers due to the pro-inflammatory state associated with increased adiposity (Xiao et al., 2023[19]). The lack of significant difference in IL10 levels suggests that the anti-inflammatory response may not be as severely impacted by obesity in PCOS as previously thought. Alternatively, it could indicate a compensatory upregulation of anti-inflammatory pathways in the presence of increased adipose tissue.

6- Conclusion

The study revealed significant differences in S. DHEAS levels between non-obese and obese women with PCOS, with non-obese women exhibiting higher levels. This suggests that BMI might influence DHEAS levels in women with PCOS, potentially affecting the syndrome's endocrine profile. However, no significant differences were found in the levels of serum TNF-α and IL10 between the non-obese and obese groups. This indicates that these inflammatory markers might not be significantly impacted by obesity in the milieu of PCOS. The results highlight the complexity of PCOS and the importance of considering BMI in its management, particularly regarding its impact on hormonal balance and inflammatory status.

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FAuthor Contribution

Huda Mahdi performed the study, and Wassan A. Al-Jubouri supervised the work .

Conflict of Interest

The authors declare no conflict of interest .

Ethical Clearance

The study was approved by the Ethical Approval Committee.

Financial Disclosure

There is no financial disclosure.

Ethical Clearance

The study was approved by the Ethical Approval Committee

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