Article

Is Interleukin-38 Diagnosis Marker for Untreated Patients with Polycystic Ovary Syndrome?

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Abstract

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects female of procreation age, it is linked to an imbalance in ovulation and hyperandrogenism, and this imbalance is accompanied by various metabolic abnormalities such as IR and obesity. It thought there are no relationship between IR in women with PCOS and body mass index (BMI), but obesity promotes IR. PCOS estimated at over 200 million women worldwide, the prevalence of PCOS is reported to be 18%, with a specific range of 17.8% ± 2.4. It's worth noting that prevalence estimates can vary based on the population studied, geographic location, and other factors. Prevalence rates without imputation were computed at 11.9%±2.4. Additionally, it was observed that PCOS impacted 28% of obese women and 5% of lean women. Certainly, the latest research revealed that the occurrence rates of PCOS based on the NIH, Rotterdam, and Androgen Excess Society (AE-PCOS) criteria were 6.1%, 19.9%, and 15.3%, respectively. This study included samples of 90 women of reproductive age (20-45 years). They were distributed into two groups, the first group included 45 patients who were diagnosed with polycystic ovary syndrome (PCOS) through the simultaneous appearance of 3-4 symptoms that are essential for diagnosis. Their ages ranged between 20-33 years old. The second group (the control group) included 45 women who were completely free of symptoms of PCOS, based on clinical and ultrasound examinations. Interleukin-38, was measured in the serum samples of the study individuals. The results of the present study showed significant (p<0.05) decrease in the levels of interleukin-38 in the samples of patients with PCOS comparison to healthy individuals. The study illustrated the sensitivity of interleukin-38 was 96%, while the specificity of interleukin-38 was 100%. The most important conclusion reached by the study is that interleukin-38 is promising tool for differentiating PCOS patients from healthy individuals.

Keywords :PCOS, Interleukin-38, Diagnostic Marker.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects female of procreation age, it is linked to an imbalance in ovulation and hyperandrogenism, and this imbalance is accompanied by various metabolic abnormalities such as (IR) and obesity [1]. It thought there are no relationship between IR in women with PCOS and body mass index (BMI), but obesity promotes IR [2]. It is a disorder in the secretion of gonadotropin LH and FSH from the anterior pituitary gland, high levels of free androgens, an increase in testosterone, and a decrease sex hormone binding globulin (SHBG) in PCOS patients. Far from increasing the risk of diabetes, metabolic syndrome, and cardiovascular disease (CVD), which occur due to IR and inflammation [3]. PCOS estimated at over 200 million women worldwide, the prevalence of PCOS is reported to be 18%, with a specific range of 17.8% $\pm$ 2.4. It's worth noting that prevalence estimates can vary based on the population studied, geographic location, and other factors [4]. Prevalence rates without imputation were computed at 11.9%$\pm$2.4. Additionally, it was observed that PCOS impacted 28% of unselected obese women and 5% of lean women. Certainly, the latest research revealed that the occurrence rates of PCOS based on the NIH, Rotterdam, and Androgen Excess Society (AE-PCOS) criteria were 6.1%, 19.9%, and 15.3%, respectively [5].

Interleukin-38is a member of the interleukin-1 (IL-1) family and the interleukin-36 subfamily. It is important for the inflammation and host defense. This cytokine is named IL-1F10 in humans and has similar three dimensional structure as IL-1 receptor antagonist (IL-1Ra). The organization of IL-1F10 gene is conserved with other members of IL-1 family within chromosome 2q13. Interleukin-38 is produced by mammalian cells may bind the IL-1 receptor type I. It is expressed in basal epithelia of skin, in proliferating B cells of the tonsil, in spleen and other tissues. This cytokine is

playing important role in regulation of innate and adaptive immunity [6].

Interleukin-38 probably originated from a common ancestral gene - an ancient IL-1RN gene [7]. This cytokine has 41% homology with IL-1Ra and 43% homology with IL-36Ra. Interleukin-38is expressed in skin, spleen, tonsil, thymus, heart, placenta and fetal liver [8]. In tissues which do not play a special role in immune response, interleukin-38is expressed in low quantity similar to other members of the IL-1 family [9]. In disease setting, especially when the activation of inflammatory response is dysregulated, the expression of interleukin-38is changed. For example, in case of spondylitis ankylopoetica CVD rheumatoid arthritis or hydradenitis supportive [10, 11].

Materials and Methods

The Population: this study was designed to include samples of women of reproductive age (20-45 years). The study included 90 women distributed into two groups. The first: 45 patients were diagnosed with polycystic ovary syndrome (PCOS) through the simultaneous appearance of 3-4 symptoms that are essential for diagnosis. Their ages ranged between 20-33 years old. The second group (the control group) included 45 women who were completely free of symptoms of PCOS, based on clinical examinations and ultrasound examinations. The ages of this group ranged between 20-45 years. Samples of women with PCOS were collected from visits to the women's wards of Al-Zahraa Teaching Hospital and Al-Furat Al-Awsat Hospital, while samples of healthy individuals were collected from women in the work environment (women working in hospitals as well as postgraduate students at the Faculty of Education for Girls - University of Kufa). The sample collection process took 4 months (from the beginning of October 2023 until the end of January 2024).

Inclusion Criteria: the patients must exhibit at least 3-4 symptoms of PCOS. They must have normal puberty and not suffer from primary amenorrhea, before

symptoms of the PCOS appear. Age of the participants (patients and controls) must be at least 20 years old, and no more than 45 years old.

Exclusion Criteria: a number of female were excluded, which included: pregnant, females (patients or controls) who use contraceptives, menopause females, females with sexual or gynecological diseases, females who underwent surgical operations (even Cesarean section) during the last two years before the current study was conducted, females patients who suffered from cancerous or chronic diseases (diabetes, cardiovascular disease, and hypothyroidism), females with autoimmune diseases, and smokers.

Sandwich enzyme linked immune sorbent assay (ELISA) was applied to determine the level of interleukin-38 in the serum samples of the study individuals, the kit was supplied by Elabscince company.

The outcomes of the present study were analyzed through the statistical package for the social sciences (SPSS) version 26 software application statistical analysis system and excel (statistical package). The variables were illustrated by mean ± S.D, minimum and maximum. Inferential data analysis includes independent *student's t-test* was applied to assess differences between the levels of interleukin-38. The probability of deflection than controls are considered statistically significant if *p-value* is below 0.05. Receiver operating characterist(ROC) curve was applied to present the sensitivity of interleukin-38.

Results and Discussion

Assessment of Interleukin-38 in the Sera Samples of the Study Groups

Interleukin-38 levels were measured in the sera of the study individuals. The results showed a significant deficiency (p=0.000) of the interleukin-38 concentration in patients with PCOS group in comparison to the those in the controls group, as shown in **Table 1.**

Table1: Levels of Interleukin-38 in the Samples of the Study Individuals

Subjects (n)	Interleukin-38 (ng/mL) Mean ± SD	Minimum-Maximum	p-value
PCOS Patients (45)	2.174±0.692	0.341-2.992	0.000
Controls (45)	3.162±0.412	1.920-4.320	

Interleukin-38 has anti-inflammatory properties like interleukin-36Ra. Several studies compared circulating interleukin-38 concentrations in healthy and diseased populations to characterize its role in both auto-immune and inflammatory pathologies, with both higher and lower concentrations being associated with certain diseases [12]. Interleukin-38 has been observed in different types of diseases such as autoimmune diseases, infections, and acute cardiovascular events [13]. Evidence of interleukin-38's acute role in response to local or systemic infections, however, is scarce. Several studies considered interleukin-38 as a disease biomarker, e.g., discriminating low and high disease activity, predicting disease progression and response to therapy treatment [14]. However, to use interleukin-38 as a biomarker in disease, reference concentrations in healthy adults must be available to determine a discriminatory value. To the best of the knowledge, no such reference has been established for interleukin-38, as each of the studies has used its own control group to determine a physiological reference circulating concentration [15]. The current study is the first of its kind to examine interleukin-38 in patients with PCOS. The results of the study indicate to decrease in the levels of interleukin-38 in patients with PCOS compared with those healthy individuals. In study on the source of the cytokines, the total number of circulating leukocytes and the distribution of eggs (lymphocytes, neutrophils, natural killer cells) in PCOS are determined. Cellular and cytokine changes are important because normal immune system function is necessary for proper

ovulation. Within the ovary, immune cells secrete local cytokines that promote follicle growth, oocyte maturation, and timely follicle rupture [16]. This impaired cytokine pattern likely plays a major role in the immunopathogenesis of PCOS. Neuro-immune axis examination can be an effective study in determining the etiology of PCOS [17]. Inteleukin-38 is closely related to pulmonary diseases, these studies have shown that inflammatory cytokines play important roles in acute respiratory distress syndrome (ARDS) showed elevated level of inteleukin-38 in patients with chronic hepatitis B, suggesting that inteleukin-38 could be used as a biomarker for liver hepatitis infection and liver injury [14] .

Sensitivity and Specificity of the Assessed Criteria

Sensitivity is known as the true positive rate or the probability of detection, it measures the proportion of positives that are correctly identified. Specificity is known as the true negative rate; it measures the proportion of negatives that are correctly identified. The receiver operating characteristic (ROC) was applied to evaluate the diagnostic efficiency of Interleukin-38 in **Figure 1**.

Table 2 shows the area under the curve (AUC) and cut-off value as well as the individual efficacy (sensitivity) and specificity of interleukin-38 to distinguish PCOS patients from healthy individuals. The study illustrated the sensitivity interleukin-38 was 96%, while the specificity of interleukin-38 was 100%.

Table 2: Receiver Operating Characteristic Analysis of Interleukin-38 as Diagnostic Marker for Polycystic Ovary Syndrome

Criteria	AUC	SE	p-value	Cutoff value	Sensitivity %	Specificity %	CI (95%)
Interleukin-38	0.975	.0160	0.000	2.957	96	100	0.944-1.000

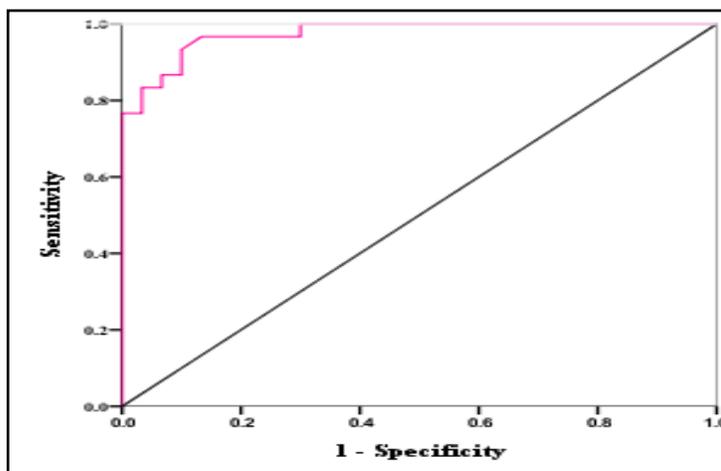*AUC: Area Under Curve, SE: Standard Error*

Figure 1: Receiver Operating Characteristic Curve of

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