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Association of certain HLA alleles, IL-6 and Estrogen levels as immunogenetic factors with incidence of ovarian cysts

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ABSTRACT

Background and Aim: Ovarian cyst syndrome, as a common female endocrinal defect at age of reproduction, it is a heterogeneous condition accompanied by clinical symptoms, including reproductive, cardio metabolic, and psychological disorders results in various diseases as consequences of immune system dysfunction, a recent study have reported that immunological mechanisms are involved in the development of ovarian syndrome. Patients with ovarian cysts have been found to be under a chronic but low-grade inflammatory status, including high levels of leukocytes, and disorder of endothelial, and pro- inflammatory cytokines. To detect any possible relation between genetic factors and immune response and hormone levels with incidence of ovarian cyst

Material and Method: a whole blood samples from 33 adult females with ovarian cysts for HLA typing by(SSO PCR) with(Auto-Lipa) (automatic line probe assay) compared with another 20 healthy control samples .Serum samples from the same patients and control groups were used for estimation of the IL-6 and Estrogen levels by ELISA test. .

Results; Genotyping of HLA region revealed a significant increase in frequency of certain alleles, *0320 and *0701 alleles showed significant P value 0.020, *730 allele with p value 0.05.IL-6 levels revealed an increase in patients group, compared to healthy control groups. Oslo estrogen levels increased in patients group compared to control group. Conclusions: There is a significant variation in various parameters between ovarian cyst patients and healthy control groups, and this indicate a serious impact of these parameters in incidence of the disease.

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1. Introduction

The Poly Cystic Ovarian Syndrome (PCOS) is a multifactorial, genetic, and metabolic disorder characterized by chronic anovulation, polycystic ovaries and biochemical and clinical manifestations of hyperandrogenism. It has a huge negative role in the and metabolism, physiology and symptom of the disease on the body as it may provoke a metabolic syndrome with insulin resistance, hyperinsulinemia, hypertension, abdominal obesity, and dyslipidemia presenting as frequent metabolic characters, such as type 2 diabetes mellitus, endometrial hyperplasia and cardiovascular disease [1]. Because several features of PCOS (polycystic ovarian syndrome) may be in evolution in adolescents, it is suggested that only firm criteria should be used to make a diagnosis of PCOS during adolescence. Hyperandrogenism, oligo menorrhea, and ovarian morphology change during adolescence [2] approximately 5-10% of women of reproductive age In utero fetal programming or dysregulation of the hypothalamic-pituitary-gonadotropic axis at crucial developmental stages, in which the syndrome is detected and mediated by the interaction of genetically determined hyperandrogenism and environmental factors, may have a significant role in the development of the final expression of the PCOS(polycystic ovarian syndrome) phenotype and its long-term consequences [3]. Familial, ethnic and racial variations in the prevalence of the syndrome are regarded [4]. Environmental, genetic and nutritional factors are involved [5]. major histocompatibility complex (MHC) a group of various human leucocytes antigens, encoded by short arm of chromosome no. six known as HLA system. These antigens, shows an extensive polymorphism [6]. These antigens or alleles were reported to have positive association with various diseases, including ovarian cyst syndrome, and the available evidences referred that this system is involved in conferring an immunogenic predisposition and prophylactic role in developing or resistance of these diseases [7, 8, 9]. IL-4 in Th2 lymphocytes, IL-1 in monocytes, IL-6 in T-lymphocytes and interferon-γ in Th1 cells, Estrogens increase the secretion of their levels and their stimulatory effect on the immune system was inhibited by progesterone [10, 11]. One of the most prevalent characteristics of the ovarian cyst syndrome is Fertility problems, which is the most frequent cause of an ovulatory infertility [12]. Owing to its phenotypic heterogeneity, ovarian cyst syndrome may occur with or without clinically ovary dysfunction. During pregnancy an increased risk of gestational diabetes mellitus, hypertension, and premature delivery has been restarted [13]. Simple cysts occur in all age groups most likely, and mixed solid cystic ovarian lesions have higher malignancy rate compared to simple cysts.

the most ovarian cysts are benign, and the most important independent ovarian cyst risk factor is the patients age, and the post-menopausal women has any type of ovarian cyst weather simple or mixed should have proper follow-up and treatment due to a malignancy higher risk [14, 15]. In most patient's ultra-sonographic findings with simple ovarian cysts do not require treatment. While, in a postmenopausal patient, a persistent simple cyst smaller than 10cm in size in the normal value of CA125 may be monitored with many repetitive ultra-sonographic examinations for long period [16]. Cyst volume according to ultra-sonographic data seems to be of little importance with respects to other aspects [17].

For the multiloculated complex cysts, the malignancy risk rises to 36% of cases. If cancer is diagnosed, regional or distant metastasis may be present in up to 70% of cases and 25% of new cases will be limited to stage I disease [18]. Mortality related with malignant ovarian carcinoma is linked to the stage at the time of diagnosis, and patients with the carcinoma be inclined to present late in the course of the disease.

Ovarian cysts in most patients are asymptomatic, and discovered incidentally during routine ultrasonography or pelvic examination. Some cysts, however, may be associated with a symptoms feature, sometimes severe [19]. While symptoms in malignant ovarian cysts mostly do not appear until they reach critical stage. Studies have shown that genetics, endocrine dysfunction, inflammation, stressful environments are the main causes of ovarian cysts in women. [20, 21] in addition to a variety of psychological disorders. For instance, the studies revealed that ovarian cysts affect the synthesis and secretion of hormones, thereby triggering depression [22]. Moreover, chronic inflammation could induce ovarian cysts. [23] Serum markers. In the presence of an ovarian mass CA1 25 has a good value for disease prediction, especially if the threshold value is elevated from 35 to 65 units/ml. even so, CA125in 50 % of first-stage carcinomas have a normal value [24]. The incidence of ovarian cysts significantly decreases as women approach the menopause in comparison to that of their reproductive years, [25], ovarian cysts remains the most common endocrine disorder among women, with various phenotypic expressions [26]. The irregular menstrual cycles, oligo menorrhea and amenorrhea, can be related to anovulation [27]. Women with ovarian cysts had increased hemoglobin levels [28]. IL-6 is a proinflammatory pleiotropic cytokine with low molecular weight protein has 185 amino acids that is produced by many cell types including lymphocytes, neutrophils, monocytes, macrophages, fibroblasts, endothelial cells, and tumor cells.[29, 30,31, 32] IL-6 is a crucial proinflamatory cytokine produced in response to local proinflammatory cytokines such as TNF-α, which is one of the main cytokines essentially expressed in majority of malignant ovarian carcinomas and induce other various cytokines, such as chemokines, antigenic factors, and transcription factors that promote spread of tumor growth and metastasis through an autocrine and paracrine manner [33]. The IL-6 effects that increased angiogenesis, invasion, and metastasis gives this potential pathway significant role in development of suppressive therapeutics model and interrupt ligand-induced activation that has been shown to be involved in ovarian cancer [34, 35]. In 2021, Pawlik et al. performed a comparative study for the clinical importance of IL-6, IL-8 and TNF-α in of ovarian carcinoma and benign ovarian tumor differentiation. Statistically significant increase of IL-8 and TNF-α levels in malignant tumors. No significant role of IL-6 in the tumors differentiation. [36]

2. Materials and Methods

Twenty-seven adult females' patients with ovarian cysts, age range 20-50 years and 20 healthy females as control, their ages were matched with the patients enrolled in this study. They were among patients admitted to AL-Kadhumyia Teaching Hospital and Baghdad medical city teaching hospital from February 2022 to September 2023. The diagnosis was made by the consultant medical staff, which was based on clinical and (X-ray and ultrasound examination). Three ml of blood were withdrawn from each subject under aseptic technique, then transferred into EDTA tube, kept at -20°C for the genotyping of HLA class I and II. The DNA was extracted by using the genome DNA extraction kit (Qi a gene/Germany). All DNA was stored at -20°C until tested. HLA-genotyping were performed by the PCR-SSO according to the manufacturer's instructions, this method depends on reverse hybridization, using the PCR-SSO kit (Histo Type/ DNA-SSO Kits-Inn genetics Line Probe Assay, INNO-LiPA, Belgium). ,

this method depend on reverse hyperdization 2ml were transmitted to plain tubes for extraction of serum to estimate the IL-6 and estrogen levels. by ELISA test: Commercial kits were utilized for estimation of serum levels of IL-6, (Demeditec Diagnostic/Germany) and using automate ELISA apparatus (Diagnostic Automation Inc, USA) and following the manual protocol supplied with the kit. The total estrogens ELISA manufactured by (Eagle Biosciences, Inc.) Is a competitive immunoassay.

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Competition occurs between total estrogens present in standards, controls and patient samples and an enzyme-labelled antigen (conjugate) for a limiting number of anti-estrogen antibody binding sites on the microplate wells. After a washing step that removes unbound materials the enzyme substrate is added and approximately 15–-20 minutes later the enzymatic reaction is terminated by addition of stopping solution. The resulting optical density (OD), measured with a microplate reader, is inversely proportional to the concentration of total estrogens in the sample. A standard curve is plotted with a provided set of standards to calculate directly the concentration of total estrogens in patient samples and controls.

3. Results and Discussion

The genotyping tests results In HLA-A region revealed a significant increase in control group of alleles frequency for *0320 allele compared with patients group 0:4 and the p. value was .021, as in the (table-1), for the HLA-B region no significant alleles frequency was reported as showed in (table- 2). The genotyping of HLA-DR region a significant alleles frequency reported; *0201 allele repeated in 9 samples of patients compared with zero in the samples of control group, the p. Value is 0.007, as in (table -3). The HLA-DQ region reflect a significant allele of *730 that appeared in 12 patients sample with zero time of appearance in healthy control samples, and the P value was 0,05, as in (table-4).

Table (1). HLA – A alleles frequency in ovarian cyst patients and healthy control

HLA-A allele	Ovarian cyst Patients(N=33)	%	Control((N=20	%	OR	EF	PF	P-Value
*0201	0	0.00%	1	5.00%	0.213	0.00	0.00	NS
*0321	4	13.33%	0	0.00%	6.962	3.43	1.41	NS
*0302	5	16.67%	2	10.00%	1.596	1.87	2.25	NS
*0503	2	6.67%	0	0.000%	3.596	1.44	3.25	NS
*0603	1	3,33%	0	0.000%	2;085	0.52	-1.08	NS
*0301	3	10.00%	3	15%	0.636	-1.71	0.63	NS
*0320	0	0.000%	4	20.00%	0.060	0.00	0.00	.021
*0303	0	0.000%	2	10.00%	0.121	0.00	0.00	NS
*0608	2	6.67%	0	0.00%	3.596	1.44	3.25	NS
*0318	2	6.67%	2	10.00%	1.541	-1.08	0.52	NS

OR; odd ratio; N; Non significant EF; Etiological factor PF; Preventive factor

Table (2). HLA –B allele's frequency in ovarian cyst patients and healthy control

HLA – B allele	Ovarian cyst Patients(N=33)	%	Control((N=20	%	OR	EF	PF	p.Value
*0103	2	6.67%	4	20.00%	0.322	-4.22	0.81	NS
*0193	4	13.33%	0	00.00%	6.962	3.43	1.41	NS
*0205	3	10.00%	0	0.00%	5.218	2.43	1.70	NS
*0206	0	0.00%	1	5.00%	0.213	0.00	0.00	NS
*0309	3	10.00%	0	0.000%	5.218	2.43	1.70	NS
**1302	2	6.67%	2	10.00%	0.649	-1.08	0.52	NS
*1832	7	23.33%	6	30.00%	0.712	-2.83	0.74	NS
*2309	0	0.00%	1	5.00%	0.213	0.00	0.00	NS
*3232	0	0.00%	1	5.00%	0.213	0.00	0.00	NS
*3524	0	0.00	1	5.00%	0.213	0.00	0.00	NS
*3551	3	10.00%	0	0,000%	5.218	0.192	2.43	NS
*3581	2	6.67%	4	20.00%	0.322	-4.22	0.81	NS
*3591	0	0.00	2	10.00%	8.243	0.00	0.00	NS
*3905	1	3.33%	1	5.00%	0.661	-0.51	0.34	NS

Table (3). HLA DR alleles frequency in ovarian cyst patients and healthy control

HLA-DR allele	Patients(N=33	%	Control((N=20|	%	OR	EF	PF	P.value
*1101	2	6.67%	4	20%	0.322	-4.22	0.81	NS
*0201	9	30.00%	0	0.00%	18.116	8.50	1.13	0.007
*0301	1	3.33%	3	15.00%	0.254	-2.93	0.75	NS
*0401	0	0.00%	2	10.00%	8.243	0.00	0.00	NS
*0501	1	3,33%	0	0.00%	2;085	0.52	-1.08	NS
*0202	3	10.00%	0	0.00%	5.218	2.43	1.70	NS
*0202	1	3.33%	2	10.00%	0.376	-1.66	0.62	NS
*0503	1	3.33%	3	15.00%	0.254	-2.93	0.75	NS
*050	3	10.00%	3	15.00%	0.636	-1.71	0.63	NS
*0602	2	6.67%	4	20.00%	0.322	-4.22	0.81	NS
*0701	2	6.67%	7	35.00%	0.158	-10.6	0.91	0.020
*0707	5	16.67%	2	10.00%	1.596	1.87	2.15	NS

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Table (4). HLA –DQ allele's frequency in ovarian cyst patients and healthy control

HLA-DQ allele	Patients(N=33)	%	Control((N=20|	%	OR	EF	PF	P.value
*0201	1	3,33%	0	0.00%	2;085	0.52	-1.08	NS
*0202	4	13.33%	2	10.00%	1.257	0.82	-4.46	NS
*0203	0	0.00%	1	5.00%	0.213	0.00	0.00	NS
*730	12	40.00%	0	0.000%	20.886	0.00	0.00	0.05
*0809	2	6.67%	0	0.000%	3.596	1.44	3.25	NS
*1359	3	10.00%	1	5.00%	1.655	1.19	6.35	NS
*1370	1	3,33%	0	0.00%	2;085	0.52	-1.08	NS

Table (5). Average levels of IL-6 and Estrogens in ovarian cyst patients compared with healthy control

Parameters	Patients	Control	P.Value
IL-6 Levels	55 pg./ml	35 pg./ml	NS
Estrogen Levels	340 pg./ml	70 pg./ml	0.05

*** Normal value of IL-6; 7 pg./ml; *Normal value of Estrogens 30-400 pg./ml; *11-20 day; 34-501 pg./ml; 21-30 day; *48-350 pg./ml; *Post-menopausal; 40-244 pg./ml**

variation in the Estrogen levels between the two studied groups P. value is 0.05, while the IL-6 reported no significant variation as itis clear in (table 5).

The present study demonstrated that HLA-A *0320 Value .021 was significantly increased in control groups compared with ovarian cyst syndrome patients, and*07 01 allele in HLA- class II; DR region with P. value 0.020 the antigen was four times more frequently observed in the controls compared to patients. Such finding may reflect the importance of such marker in PCOS of Iraqi females. And in a statistical interpretation the value may represent these alleles could be considered as a prophylactic factor that provide resistance against occurrence of the disease etiology due to such allele [37]. While, the DQ region showed a highly increase in allele frequency since the *730 allele highly increased in patients group compared with healthy control group with significant p. Value =0.05. This could be considered as a predisposing factor of the syndrome and disease associated allele.

Immunogenic marker for PCOS in Iraqi Arab populations. Inspecting HLA antigen frequencies in other world populations of PCOS revealed different observations. In Japanese patients, an increased frequency ofHLA-B54 has been reported [38, 39]. Whereas, in Chinese patients the disease was positively associated with HLA-B46.Early studies in Caucasian PCOS patients were also conflicting, but two studies suggested that HLA-B7 is positively associated with the disease [39, 40], The differences between studies may be related to racial variation but nearly all studies reveal a proposed role for the increase in frequency of certain alleles in patients group compared to healthy control groups.

The levels of IL-6 in ovarian cyst patients showed an increase in serum levels compared with healthy control group but the difference is not statistically significant, this may reflect a minor role for this cytokine in disease pathogenesis. the levels of serum total Estrogen revealed a significant increase in patient's groups compared with healthy control and this may reflect the major role of this hormone in the disease pathogenesis. Although it is generally accepted that E/progestin treatment prevents the formation of functional ovarian cysts, [41] remains little evidence that these medications are effective in hastening the disappearance of these cysts once they are formed. Although the morbidity involved with a brief trial of hormonal therapy is generally considered to be low, patients who receive this treatment and subsequently undergo exploratory surgery for a persistent adnexal cyst may be at increased risk for postoperative thromboembolism. [42,43]

4. Conclusions

HLA-A *0320 allele significant increase in control group. HLA-DR; *0201 allele and, HLA-DQ *730 allele significant increase in ovarian cyst patients pointed to the important role of the genetic factors in both resistance and predisposing to the infection through certain alleles which practice its impact via the proinflamatory cytokines. Also significant increase in the patients estrogen hormone levels.

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