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L-SELECTIN, CLEC6AAND GALECTIN-16 AS NEW BIOCHEMICAL TOOLS FOR DIAGNOSIS OF UNTREATED PATIENTS WITH PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is currently recognized as a complex heterogeneous disease characterized by hyperandrogenism, amenorrhea, oligomenorrhoea, an ovular infertility, and ovarian polycystic syndrome with a range of phenotypic and demographic variations. PCOS is among the most common endocrine disorders in women. Its diagnostic and phenotypic complexities present significant challenges to the clinical and basic research community. this study included samples of 90 women of reproductive age (20-45 years). They were distributed into two groups. The first: 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 examinations and ultrasound examinations. Sandwich-ELISA technique was applied to determine the level of L-Selectin, CLEC6A and Galectin-16 in the serum samples of the study individuals. The results of the present study showed a significant (p=0.000) decrease in the levels of L-Selectin in the samples of patients with PCOS comparison to healthy individuals. The study proved that there were significant differences (p=0.000) between the two study groups, as an increase in CLEC6A level was observed in the diseased group compared to the healthy group, while no significant differences (p=0.612) in the levels of galectin-16 in PCOS patients and the control group. The relation between CLEC6A and Galectin-16 was statistically (p=0.016) negative in ~76% of PCOS patients, while the study indicates that CLEC6A is associated with galectin-16 with a positive significant relationship in approximately 79% of the control group members. From the current work, it can be concluded that both L-Selectin and CLEC6A can be excellent diagnostic tools for PCOS. Moreover, evaluating the relationship between CLEC6A and galectin-16 to definitively predict the possibility of a female suffering from polycystic ovary syndrome when the result of testing the relationship between the two parameters isnegative.

Key Words PCOS, L-Selectin, CLEC6A and Galectin-16

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

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(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% ± 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%±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].

L-Selectin and its ligands participate in the adhesion of the blastocyst to the endometrium at the maternal–fetal interface. P-selectin and E-selectin are involved in immune recognition of maternal decidua to the embedded embryo as well as trophoblast migration within decidual spiral arterioles. Moreover, altered expression of selectins and their ligands are found to be associated with some abnormal pregnancies and infertilities[6]. L-Selectin, also known as CD62L, is a cell adhesion molecule found on the cell surface of leukocytes, and the blastocyst. It is coded in humans by the *SELL* gene. L-Selectin belongs to the selectin family of proteins, which recognize sialylated carbohydrate groups containing a Sialyl LewisX (sLeX) determinant[7]. L-Selectin plays an important role in both the innate and adaptive immune responses by facilitating leukocyte-endothelial cell adhesion events[6]. These tethering interactions are essential for the trafficking of monocytes and neutrophils into inflamed tissue as well as the homing of lymphocytes to secondary lymphoid organs[8]L-Selectin is also expressed by lymphoid primed hematopoietic stem cells and may participate in the migration of these stem cells to the primary lymphoid organs[9]. In addition to its function in the immune response, L-Selectin is expressed on embryonic cells and facilitates the attachment of the blastocyst to the endometrial endothelium during human embryo implantation[10].

C-Type Lectin Domain Family 6, Member A (CLEC6A) is a member containing 6Atype II transmembrane protein superfamily with an extracellular carbohydrate recognition domain[11]. The gene is responsible for encoding this protein in humans. It is the encoded protein that has a role as a pattern recognition receptor that recognizes alpha-mannans, for example, it plays a role in the innate immune response to fungi[12]. It notices an increase in its levels when inflammation is stimulated. It works to balance serum protein levels and also regulates interactions between cells by binding internal adhesion molecules. CLEC6A is a member of the C-type lectin/C-type lectin-like domain (CTL/CTLD) superfamily[13].

Galectin-16 is a recently discovered galectin, whose global structure has remained unknown [14] Although galectin-16 gene was described more than 10 years ago[15], the regulation, functions, and clinical aspects of this tissue-specific molecule are largely unexplored. Primary association of *LGALS16* with placental tissue has been challenged by its detection in brain tissues and several cancer cell lines as followed from available microarray and RNA-seq databases. There are bioinformatics indications that the expression of *LGALS16* changes in association with Alzheimer's disease, chronic myeloid leukemia, breast cancer, B-cell lymphoma, and T2DM [16] Although *LGALS16* was not significantly impacted at the gene level in preeclampsia, there remain questions regarding regulation at the protein level, which cannot be properly addressed at this time due to the absence of commercially available specific galectin-16 antibodies. The results obtained with recombinant galectin-16 are promising, but there is still a gap in the understanding of why the expression of endogenous galectin-16 protein has not

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been reported[17]Nevertheless, among the possible functions of galectin-16 in these and other tissues, its contribution to the regulation of cellular differentiation and programmed cell death (apoptosis) warrants special attention. Lastly, the use of proper cell culture models and the examination of multiple factors (transcription regulators and miRNA) is evidently the first line of study to position galectin-16 within a complex galectin network in cells[18].

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 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 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**.**

Assessment of Lectins Concentration: sandwich enzyme linked immune sorbent assay (Sandwich-ELISA) method was applied to determine the level of L-Selectin, CLEC6A and Galectin-16in the serum samples of the study individuals.

The Statistical Analysis of the Data: 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, maximum, frequencies, and percentages. Inferential data analysis includes independent student's t-test was applied to assess differences between the levels of the studied parameters. Pearson's correlation was applied to determine the relation among the parameters of the present work. The probability of deflection than controls are considered statistically significant if p-value is below 0.05.

Results and Discussion

Assessment of L-Selectin in the Sera Samples of the Study Groups: L-Selectin levels were evaluated in the samples of patient and healthy individuals of the current work, then the outcomes were

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analyzed statistically using independent student's *t*-test. The results of the present study showed a significant (p=0.000) decrease in the levels of L-Selectin in the samples of patients with PCOS comparison to healthy individuals, as shown in **Table 1.**

Table 1: L-Selectin in Polycystic Ovary Syndrome Patient and Control Groups

Subjects (n)	L-Selectin(ng/mL) Mean ± SD	Minimum-Maximum	*p-value*
PCOS Patients (45)	4.607±1.332	0.534-6.480	**0.000**
Controls (45)	6.789±0.712	5.787-9.091	

The difference is considered significant at p<0.05.

Selectin shares several common extracellular domains with its family members, E-, and P-Selectin[19]. L-Selectin plays an important role in embryo implantation during human pregnancy. Decreased epithelial expression of ligands has been associated with infertility, while increased expression L-Selectin has been implicated in the ectopic pregnancies [20]The correlation was observed between L-Selectin levels and the presence of extra medullary disease, this observation suggests that blast cells which shed high levels of L-Selectin have a higher propensity to migrate into lymph nodes, spleen, or liver. L-Selectin plays a major role in regulating lymphocyte attachment to high endothelial venules of peripheral and mesenteric lymph nodes [21].L-Selectin ligands can be on the endothelium of inflamed tissues. Specifically, vascular L-Selectin ligands are expressed at cutaneous sites of chronic inflammation, acute dermatitis, rheumatoid arthritis, diabetes, and asthma. In addition, activation of endothelial cell cultures with proinflammatory cytokines such as tumor necrosis factor-α (TNFα) induces L-Selectin ligand expression and increased L-Selectin-dependent leukocyte adhesion [22].L-Selectin plays a vital role in the complex process of leukocyte recruitment, by functioning as both an adhesion and signaling molecule, L-Selectin contributes to both the early adhesive events as well as the later stages of chemotaxis and cell migration. L-Selectin ligand expression at sites of inflammation results in L-Selectin playing an important role in the development of autoimmune and chronic inflammatory diseases[23]. However much remains to be defined concerning the L-Selectin function, for example, despite the identifications of numerous different ligands recognized by L-Selectin, little evidence for a physiologic role for any of these molecules exists[22].The average leukocyte will express ~50,000–70,000 molecules of L-Selectin at the plasma membrane. Numerous reports have shown that L-Selectin is anchored on finger-like projections called microvilli, which increases tethering efficiency during recruitment. Protein expression of L-Selectin is constitutive on most circulating leukocytes and is slowly turned over at the plasma membrane through a process of ectodomain shedding (commonly referred to as “shedding”). A variety of artificial or physiological agonists of cell activation can, within minutes, promote robust L-Selectin shedding in numerous leukocyte sub-types. The zinc-dependent metalloproteinase, a disinterring and metalloproteinase (ADAM)17, is the major enzyme responsible for L-Selectin shedding in leukocytes. However, ADAMs 8 and 10 have also been reported to cleave

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L-Selectin in specific settings. From a clinical perspective, the soluble circulating form of L-Selectin (released because of ectodomain shedding) is sometimes used as a surrogate plasma/serum biomarker for leukocyte activity triggered during acute or chronic inflammation[24].The present study showed significant decrease inthe levels of L-Selectin at PCOS group, this result may be related to involves significant hormonal imbalances, particularly elevated levels of androgens. These hormonal changes can affect the immune system and the expression of various cell surface molecules. The current study is the first of its kind to evaluate L-Selectin in women with PCOS.

Evaluation of C-Type Lectin Domain Family 6, Member A Levels in the Study Groups: the concentration of C-Type Lectin Domain 6 family, member A (CLEC6A) was measured in the sera of females suffering from PCOS and females of the control group. The study proved that there were significant differences (p=0.000) between the two study groups, as an increase in CLEC6A level was observed in the diseased group compared to the healthy group, as shown in **Table 2**.

Table 2: Levels of C-Type Lectin Domain Family 6, Member A in the Samples of Study Individuals

Subjects (n)	CLEC6A (pg/mL) Mean ± SD	Minimum-Maximum	*p-value*
PCOS Patients (45)	226.451±17.560	202.613-272.586	0.000
Controls (45)	159.360±48.403	11.184-205.921	

CLEC6A: C-Type Lectin Domain Family 6, Member A and the difference is considered significant at p<0.05.

CLEC6A is a C-type lectin expressed by dendritic cells (DC), macrophages, and inflammatory monocytes. It is a type II membrane receptor, with a short cytoplasmic tail, and a C-terminal C-type lectin domain. CLEC6A is a receptor for high specificity to mannose structures and mediates cytokine production from DC and other antigen presenting cells. CLEC6A gene is located on human chromosome 12[25].The current study is the first of its kind to evaluate CLEC6A in females with PCOS. There is no study to evaluate it in any gynecological. The results of the study indicate an increase in its levels in patients with PCOS could be influenced by chronic inflammation. PCOS is associated with a state of chronic low-grade inflammation. Increased levels of CLEC6A may reflect an up-regulation of immune responses as part of the body's attempt to manage this persistent inflammatory state[26]. Also, may be cause oxidative stress is commonly observed in PCOS. Oxidative stress can influence the expression of immune receptors and other molecules involved in the inflammatory response. It can lead to the activation of pathways that upregulate CLEC6A expression[27].

Evaluation of Galectin-16 in The Sera Samples of The Study Groups: Galectin-16 levels were estimated in serum samples of participants in the current study. **Table 3**shows that there are no

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significant differences (p=0.612) in the levels of galectin-16 in PCOS patients and the control group.

Table 3: Levels of Galectin-16in the Samples of the Study Individuals

Subjects (n)	Galectin-16 (pg/mL) Mean ± SD	Minimum-Maximum	*p-value*
PCOS Patients (45)	18.779±4.776	1.450-25.403	**0.612**
Controls (45)	20.652±4.770	4.217-26.760	

The difference is considered significant at p<0.05.

Galectin-16is a monomeric protein, which is composed of 142 amino acids and has a typical galectin structure of the CRD β-sandwich with two sheets formed by six β-strands on the concave side (S1–S6) and five β-strands on the convex side (F1–F5) [18]*LGALS16* SNP was revealed to be associated with insulin secretion in a cohort of African Americans, the study showed that interactions between *LGALS16* SNP and others such as an intergenic SNP upstream of the *LYPLAL1* gene, have also been associated with T2D risk[28]The levels of galectin-16 were evaluated in Iraqi patients with thyroid disorders, and this study showed that the production of this protein stops completely in people with hypothyroidism, while its levels in patients with hyperthyroidism were close to those observed in the control group[29].In another study (in progress) designed to estimate galectin-16 levels in women with breast tumors who are undergoing chemotherapy (Doha's Study), the results of that study indicate that galectin-16 levels are increased in women with breast cancers, while its levels in women with benign breast tumors are approximately the same. For women in the control group. Moreover, the results of Doha's study show that receiving chemotherapy works to suppress the production of galectin-16 and return it to normal levels, after completing the treatment program recommended by the specialist doctor[30]The current study is the first of its kind to estimate galectin-16 concentration in the cases with PCOS. The results of this study indicated that the levels of galectin-16 in patients with PCOS were among the levels of the control group. This indicates that the production of galectin-16 is not affected by the changes associated with excessive production of ovarian hormones which may be due to the hypothesis that the path of production of this protein may be disrupted as a result of changes that support excessive storage of energy resources, increase in fat mass, suppression of energy consumption and limit it to minimal limits only, while galectin-16 works to enhance the path of cell death programming, galectin-16 has also been proven to urge the programmers of cells for cells[31]

The Relationship among the New Evaluated Parameters in the Study Individuals: the relationships among the new evaluated criteria (L-Selectin, CLEC6A, and Galectin-16) were tested for the members in the study groups**.**

Relationship among the New Evaluated Parameters in the Group of Patients withPolycystic Ovary Syndrome: when potential relationships were evaluated among the new criteria in the patients

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individuals, the relation between CLEC6A and Galectin-16 was statistically (p=0.016) negative in ~76% of PCOS patients **(Table 4**).

Table 4: Correlation among the New Marks in the Group of Patient with Polycystic Ovary Syndrome

Parameters *r* *p*	L-Selectin	CLEC6A	Galectin-16
L-Selectin	-		
CLEC6A	-0.186 0.221	-	
Galectin-16	-0.076 0.620	**-0.759*** **0.016**	

***Correlation is significant at the 0.01 level, *Correlation is significant at the 0.05 level*

The interaction investigation can provide valuable visions of the disease mechanisms. The current study is the first of its kind to evaluate the relationship between CLEC6A and galectin-16 in patients with PCOS. The result significant negative correlation between CLEC6A and galectin-16. In summary, *LGALS16* gene is an interesting with tissue-specific expression in the placenta, while CLEC6A is an immune receptor involved in pathogen recognition. Investigating their interaction can provide valuable insights into cellular responses and immune regulation.

Relationship among the New Evaluated Parameters in the Healthy Group: the results of the current study indicate the absence of statistical significance from the correlations among the evaluated parameters (L-Selectin, CLEC6A, and Galectin-16) in the healthy group except what was recorded between CLEC6A and galectin-16. **Table 5** indicates that CLEC6A is associated with galectin-16 with a positive significant relationship in approximately 79% of the control group members. Evaluation of the relationship between CLEC6A and galectin-16 can be used to predict the possibility of a female suffering from PCOS when the relationship test result between the two parameters is negative.

Table 5: Correlations among the New Criteria in the Healthy Groups

Parameters *r* *p*	L-Selectin	CLEC6A	Galectin-16
L-Selectin	-		
CLEC6A	-0.134 0.386	-	
Galectin-16	-0.012	**0.787****	-

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	0.936	**0.001**	

*****Correlation is significant at the 0.01 level, *Correlation is significant at the 0.05 level***

The present study is the first of its kind to evaluate the relationship between assessed parameters (L-Selectin, CLEC6A, and Galectin-16) in the healthy group.

Conclusions

It can be concluded that both L-Selectin and CLEC6A can be excellent diagnostic tools for PCOS. Moreover, evaluating the relationship between CLEC6A and galectin-16 to definitively predict the possibility of a female suffering from polycystic ovary syndrome when the result of testing the relationship between the two parameters is negative.

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