Iraqi JMS

Published by Al-Nahrain College of Medicine
P-ISSN 1681-6579
E-ISSN 2224-4719
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-alnahrain.edu.iq
http://www.iraqijms.net
Iraqi JMS 2017; Vol. 15(4)

Serum Levels of Glycodelin A and Soluble Intracellular Adhesion Molecule-1 as Biomarkers for Endometriosis

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Abstract

Background Endometriosis is a benign chronic disease, characterized by the presence and proliferation of functional endometrial gland and stroma outside the uterine cavity.

Objective To evaluate the usefulness of intracellular adhesion molecule-1 (ICAM-1) and Glycodelin (Gd) as a biomarker for the diagnosis of endometriosis and to help in detection of various stages of endometriosis.

Methods Forty-four patients with endometriosis and 35 apparently healthy women as control were enrolled in this study from November 2015 to April 2016. All individuals were subjected to blood sampling for measuring their serum ICAM-1 and Gd A level by using enzyme linked immune sorbent assay technique.

Results The current study revealed significantly higher serum levels of ICAM-1 and Gd in patients group in comparison with healthy control. In addition, the sensitivity and specificity for ICAM-1 and Gd A in serum were 61%/ 66%, 76%/ 85% respectively.

Conclusion The ICAM-1 and Gd A level in serum may be useful as noninvasive test for diagnosis of endometriosis in all stages.

Keywords Endometriosis, ICAM-1, Glycodelin

Citation Draj HA, Abbas AA, Abdullah TH. Serum levels of Glycodelin A and Soluble Intracellular Adhesion Molecule-1 as biomarkers for endometriosis. Iraqi JMS. 2017; Vol. 15(4): 345-349. doi: 10.22578/IJMS.15.4.4

List of abbreviations: ELISA = Enzyme linked immune sorbent assay, Gd = Glycodelin, ICAM-1 = Intracellular adhesion molecule-1, LAF-1 = Lymphocyte function association antigen-1

Introduction

Endometriosisis a chronic gynecologic disorder defined by the kind of tissue lines the uterus known endometrial tissue also grows in other part of the body [(1)]. The disease exhibits a broad spectrum of clinical signs and symptoms and often present vexing clinical management problems for women and their physicians [(2)]. Soluble intercellular adhesion molecule-1 (sICAM-1) represents a circulating form of ICAM-1 that is constitutively expressed or is inducible on the cell surface of different cell lines. It serves as a counter-receptor for the lymphocyte function-associated antigen (LFA-1). Interaction between sICAM-1, present on endothelial cells and LFA-1 facilitates leukocyte adhesion and migration across the endothelium. sICAM-1 and its circulating form have been implicated in the development of any number of diseases [(3)]. Levels of the sICAM-I have been suggested to elevate during early stages of endometriosis (I-II) and decrease at stage (III-IV) [(4)]. Glycodelin (Gd), an endometrium-derived protein with known angiogenic, immunosuppressive,

contraceptive effects, could contribute to the development of endometriosis and endometriosis-associated infertility [5]. Moreover, Gd is not only produce in the glandular epithelium of secretary endometrium [6,7], but also is shed from endometriotic lesion into the peritoneal fluid and serum. Increase plasma glycodelin levels have been observe in patients with endometriosis [8].

The biomarkers that are simple to measure could help clinician to diagnose or at least exclude endometriosis; it might also allow monitor the treatment effect. A precise blood or urine test could avoid the need for an invasive procedure (9).

The current study aimed to evaluate the usefulness of ICAM-1 and Gd A as a biomarker for the diagnosis of endometriosis and to help in detection of various stages of endometriosis.

Methods

Forty-four women with endometriosis diagnosed by laparotomy or laparoscopy investigations confirmed by histopathological report were involved in the current study, their age range from 18 to 48 years. They were collected from Aum Albanin Center for Infertility at Al-Imamein Al-Kadhimein Medical City and from Higher Institute of Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University from November 2015 to April 2016. They were classified by a gynecologist according to the American Fertility Society (now the American Society for Reproductive Medicine; ASRAM) into different stages (minimal, mild, moderate and severe endometriosis).

In addition, the current study included 35 apparently healthy volunteers whose ages were matched with patients group, were considered as control. All of these healthy women were a symptomatic with regular menstrual cycle and fertile.

Five ml of venous blood was drawn from each patient and control. Blood sample was collected in glasses gel tubes for serum separation. The serum sample was divided in to aliquots, and kept in deep freeze till used. The measurement of serum sICAM-1 and Gd was done by ELISA technique according to instructions manual by Human Company/ Germany in Education Labs / Medical City. Ethical approval and informed consent were obtained from each participant in this study according to the declaration of Helsinki-ethical agreement, it was obtained from the Institutional Review Board of College of Medicine, Al-Nahrain University.

Results

The age of patients with endometriosis ranged between 18 to 48 years with a mean age 30.54±8.39 years while the mean age of healthy women was 33.92±14.7 as shown in table (1).

Table 1. Comparison between patients group and control group according to the age by unpaired t test

Parameter	Patients N=44 Mean±SD	Control N=35 Mean ±SD	P value
Age (yr)	30.54+8.39	33.92+14.7	0.192

The current study revealed significantly higher serum levels of Gd A and sICAM-1 in patients group in comparison with control group (Table 2).

Regarding ELISA technique was showed acceptable sensitivity and specificity of sICAM-1 and Gd A were (61%/66%) and (76%/85%) respectively (Table 3).

The comparison of serum level of parameters (ICAM-1 and Gd) according to stages of disease showed no important difference among patients group (Table 4).

Table 2. Comparison between patients and control groups according to serum level of sICAM-1 and Glycodelin by Mann Whitney U test

Parameters	Patients N=44 Median (Range)	Control N=35 Median (Range)	P value
sICAM1 (ng/ml)	98 (65-191)	92.5 (84-113)	0.005
Glycodelin (ng/ml)	135 (60-240)	92 (0-160)	< 0.001

Table 3. Sensitivity and specificity percentage of ELISA test regarding ICAM-1 and Glycodelin

Parameters	Sensitivity	Specificity	Cutoff value
ICAM1 (ng/ml)	61.9%	66.7%	95.5
Glycodelin (ng/ml)	76.2%	85.7%	99.5

Table 4. Comparison the level of parameters according to stage of Endometriosis in patients group

Parameters	Stage 1 N=4 Mean±SD	Stage 2 N=9 Mean±SD	Stage 3 N=13 Mean±SD	Stage 4 N=18 Mean±SD	P value
ICAM1 (ng/ml)	110.14±36.15	91.63±11.84	108.45±11.38	99.06±9.38	0.113
Glycodelin (ng/ml)	163.67±60.73	120.38±29.49	125.69±34.36	136.67±46.39	0.249

Discussion

Mean levels of sICAM-1 appeared significantly increase in patients with endometriosis with sensitivity and specificity (61-66%) respectively, because sICAM-1 one of the major adhesion molecules that inhibits natural killer cell-mediated cytotoxicity, resulting in defective immune surveillance, it is involved in the implantation and development of endometriotic lesions. To date, studies have shown an increase or decrease, of sICAM-1 levels (plasma/serum) in women with endometriosis compared with controls. In addition, no significant differences of sICAM-1 levels have been reported. This discrepancy may be due to different study designs, ELISA kits, or types of blood specimens, or to varying phases of the menstrual cycle [10].

Barrier and Sharpe-Timms in 2002 showed significant aberrations in levels ofICAM-1 in women with stage III and IV of endometriosis. These findings might shed light on the pathogenesis of endometriosis and be useful in the development of biochemical markers for disease stage [11].

Significant aberrations in levels of circulating adhesion molecules were found in women with stage III and IV endometriosis. These findings might shed light on the pathogenesis of endometriosis and be useful in the development of biochemical markers for disease stage [12]. Although the present study tends to support a role of sICAM-1 in the

development of endometriosis, serum concentrations of this molecule do not seem to be an effective indicator for the diagnosis of either the early or advanced stage of endometriosis. Other researchers give an idea about a panel of five biomarkers (CA-125, vascular endothelial growth factor (VEGF), Annexin V, Gd, and sICAM-1)), May et al. in 2010 [13] showed a sensitivity of 74-94% and a specificity of 55-75%. These results should be prospectively evaluated. Steff et al. in 2004 [14] have another opinions, serum levels of sICAM-1 during the luteal phase of the cycle are not able to discriminate women suffering from endometriosis from control. When confounders are taken into account, these results underline the importance of careful identification of confounders, based on patients' demographic and clinical data in studies aiming at discovering diagnostic markers for endometriosis.

Increased plasma Gd A levels have been observed in patients with endometriosis in this case-control study the sensitivity and specificity of the test by this marker are 76%, 85% respectively. Gd A with known angiogenic, immunosuppressive, and contraceptive effects, could contribute to the development of endometriosis and endometriosis-related infertility [7], this result is incompatible to others like Vdolazkaia et al. 2012 who have been conducted a study to assess the level of GdA, which found in high serum level in women with endometriosis (n=57) in comparison with control group undergoing sterilization or having ovarian cyst (n=42) the sensitivity of this test was 82.1% and specificity 78.4% that proposed the possible use of Gd A with panel biomarker for the diagnosis ultrasound-negative endometriosis[15].

Regarding Gd A, other study was adapted this, which proved that adolescent girls with endometriosis had significantly higher peritoneal fluid levels of IL-6, TNF-α and Gd A. Peritoneal IL-6, TNF-α and Gd A provided a good method of discrimination between subjects with endometriosis and controls. Using cut-off points for peritoneal fluid IL-6 (90.0 pg/mL), TNF-α (3.0 pg/mL) and Gd A (60.0 ng/mL), with high odds ratios (10.2; 14.6; 2.2) were obtained in the prediction of endometriosis in adolescents [16].

Moreover, Gd A is not only produced in the glandular epithelium of secretory endometrium, but also is shed from endometriotic lesions into the peritoneal fluid and serum. Increased plasma glycodelin levels have been observed in patients with endometriosis [17].

In conclusion, Gd A and sICAM-1in serum may be useful as noninvasive test for diagnosis of endometriosis in all stages. Further study with large sample size can be recommended to confirm this result.

Acknowledgments

The authors sincerely thank the patients for participating in this work.

Authors Contribution:

Daraj: Data collection and drafting of the article. Dr. Abbas: Design of the work, data interpretation, drafting and critical revision of the article. Dr. Allaa: samples collection.

Conflict of interest

The authors declare no conflict of interest.

Funding

Self-funding.

References

1. Fritiz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. USA: Lippincott Williams and Wilkins; 2010. p. 1221-31.
2. Giudice LC, Kao LC. Endometriosis. Lancet. 2004; 364(9447): 1789-99. doi: 10.1016/S0140-6736(04)17403-5.
3. Viganó P, Pardi R, Magri B, et al. Expression of intercellular adhesion molecule-1 (ICAM-1) on cultured human endometrial stromal cells and its role in the interaction with natural killers. Am J Reprod Immunol. 1994; 32(3): 139-45.
4. Stavreus-Evers A, Mandelin E, Koistinen R, et al. Glycodelin is present in pinopodes of receptive-phase human endometrium and is associated with down-regulation of progesterone receptor B. Fertil Steril. 2006; 85: 1803-11. doi: 10.1016/j.fertnstert.2005.12.018.

5. Bohn H, Kraus W, Winckler W. New soluble placental tissue proteins: their isolation, characterization, localization and quantification. Placenta Suppl. 1982; 4: 67-81.
6. Koistinen H, Koistinen R, Dell A, et al. Glycodelin from seminal plasma is a differentially glycosylated form of contraceptive glycodelin-A. Mol Hum Reprod. 1996; 2(10): 759-65.
7. Seppälä M, Koistinen H, Koistinen R, et al. Glycodelin in reproductive endocrinology and hormone-related cancer. Eur J Endocrinol. 2009; 160(2): 121-33. doi: 10.1530/EJE-08-0756.
8. Julkunen M, Koistinen R, Sjöberg J, et al. Secretory endometrium synthesizes placental protein 14. Endocrinology. 1986; 118: 1782-6. doi: 10.1210/endo-118-5-1782.
9. D'Hooghe TM, Mihalyi AM, Simsa P, et al. Why we need a noninvasive diagnostic test for minimal to mild endometriosis with a high sensitivity. Gynecol Obstet Invest. 2006; 62(3): 136-8. doi: 10.1159/000093120.
10. Wu MY, Ho HN. The role of cytokines in endometriosis. Am J Reprod Immunol 2003; 49(5): 285-96.
11. Barrier BF, Sharpe-Timms KL. Expression of soluble adhesion molecules in sera of women with stage III and IV endometriosis. J Soc Gynecol Investig. 2002; 9(2): 98-101.
12. Matalliotakis IM, Vassiliadis S, Goumenou AG, et al. Soluble ICAM-1 levels in the serum of endometriotic patients appear to be independent of medical treatment. J Reprod Immunol. 2001; 51(1): 9-19.
13. May KE, Conduit-Hulbert SA, Villar J, et al. Peripheral biomarkers of endometriosis: a systematic review. Hum Reprod Update. 2010; 16(6): 651-74. doi: 10.1093/humupd/dmq009.
14. Steff AM, Gagné D, Pagé M, et al. Concentration of soluble intercellular adhesion molecule-1 in serum samples from patients with endometriosis collected during the luteal phase of the menstrual cycle. Human report, 2004; 19(1): 172-8.
15. Vodolazkaia A, El-Aalamat Y, Popovic D, et al. Evaluation of a panel of 28 biomarkers for the non-invasive diagnosis of endometriosis. Hum Reprod. 2012; 27(9): 2698-711. doi: 10.1093/humrep/des234.
16. Candiani GB, Danesino V, Gastaldi A, et al. Reproductive and menstrual factors and risk of peritoneal and ovarian endometriosis. Fertil Steril. 1991; 56(2): 230-4.
17. Koninckx PR, Riittinen L, Seppala M, et al. CA-125 and placental protein 14 concentrations in plasma and peritoneal fluid of women with deeply infiltrating pelvic endometriosis. Fertil Steril. 1992; 57(3): 523–30.

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Received Jan. 22nd 2017
Accepted Apr. 24th 2017