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Evaluation of Adipose Tissue Hormones and Tumor Necrosis Factor in Patients with Endometriosis

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Abstract
Objective: To evaluate levels of physiological parameters (Testosterone, follicle stimulating hormone FSH, luteinizing hormone LH, leptin and tumor necrosis factor TNF-α, Adipsin and Ghrelin), Total antioxidant capacity-TAC, Glutathione S transfers -GST in sera of patients with endometriosis.
Methods: This study involved (85) women within reproductive age (25–40) years, who were distributed into two groups: patients´ group (55) women diagnosed with endometriosis, and (30) healthy control women. The study was carried out at Al-Karkh Maternity Hospital/ Baghdad and extended from 20/4/2024 to 20/5/2024. The pathological cases of patients were diagnosed by clinical examinations and confirmed by specialist physician with ultrasound examination. Blood samples were taken from both groups, serum was separated for each individual by a centrifuge.
Results: A significant rise in the (FSH, Leptin, TNF-α, Adipisin) while a significant decrease in levels of (Testosterone , LH, GST, TAC, Ghrelin) concentration were found in the sera of patients compered to healthy women , with a probability of $P \leq 0.05$. According to Receiver operating characteristic (ROC) statistical analysis, Area under curve (AUC) for LH, leptin, TNF-α, adipsin, ghrelin, GST, TAC were closely or equal to (1) for patients .
Conclusion: Serum levels of LH, Leptin, Adipisin, Gherlin, TNF-α and GST can be dependable as prognostic indicator markers that reflect the degree of oxidative stress accompanying endometriosis.
Keywords: Endometriosis, leptin, TNF-α, Adipsin, Gherlin, TAC, GST, ROC

Introduction

Endometriosis was estimated to affect 6%–10% of female at reproductive age. This chronic, neuronal-inflammatory condition is associated with debilitating chronic pelvic pain.[1] Clinically, this gynecological disorder is characterized by the presence of endometrial tissue outside the uterus lumen denominated as ectopic endometrium. These endometriotic lesions are commonly localized in the peritoneum, covering ovaries, uterosacral ligaments and rectovaginal septum.[2] A little information about the specific pathogenesis and regulatory mechanism of this disorder is available. Nevertheless, most studies revealed that inheritance and environment are the main factors involved in the pathogenesis. Whereas, the associated pain is resulted from nervous system- and neuroendocrine related mechanisms.[3]

A group of cytokines family mainly secreted from adipocytes known as Adipocytokine (or adipokine), might be among the biomolecules that mediate the adiposity and emergence of endometriosis or its progression. A variety of biological roles are achieved by these biomolecules such as immune mediators, regulation of cell survival, inflammation, and angiogenesis, which are also crucial functions in endometriosis establishing and progress.[4] Leptin is a member of adipokine related to endometriosis. This hormone is secreted by adipose tissue and small intestinal cells to regulate energy balance in proportion to triglycerides across certain neural pathways mainly hypothalamus to prevent hunger in which then, leading to decreases in fat storage by adipocytes.[5] Leptin was first detected in 1994 as an adipocytokine that regulate body weight, food intake, fat mass, in addition to its important regulatory role in the immune and neuroendocrine systems. It also has an important role in hormonal metabolism and regulation.[6] Recently, the role of leptin and leptin signaling in the pathogenecity of endometriosis has been detected by Kim[7] in a study on mice model. An adipokine composed of 28-amino residue peptide predominantly produced by the stomach is called ghrelin. While, fewer amounts considerably, were detected in bowel, pancreas, kidneys, the immune system, placenta, testes, pituitary, lung, and hypothalamus.[8] This factor possesses variety of physiological effects upon all body systems and contributes multitude of functions in both physiological and pathological conditions. It affects both endocrine and exocrine glands in addition to its activating role in the production of many hormones by the endocrine system.[9]

Adipsin, is a major protein of adipose cells also was involved in this study. It was first described as an adipokine in 1987 and it was then identified as complement factor D which stimulates the rate-limiting step of complement activation through the alternative pathway. Adipsin ironically decrease in many animal models with obesity or diabetes. Suggesting an extreme important role of this factor in maintaining the functions of insulin-secreting pancreatic β cell. However, its function in relation to systemic metabolism and energy homeostasis was vague.[10,11] Results obtained from a study conducted by Milek[12] suggested that adipsin serum concentrations are strongly related to obesity and age.

Tumor necrosis factor alpha (TNF-α), is a cytokine with multitude functions that has a well-established immunological roles in both innate and adaptive immunity and in the natural physiological functions of immune cells.[13] This pro-inflammatory cytokine is released by different cell-types in particular, by macrophages and lymphocytes. It can also be produced by adipose tissue although this action is weak in humans.[14] A statement of imbalance between reactive oxygen

species (ROS) and antioxidants is known as oxidative stress. Nowadays, it is widely accepted that this phenomenon may be implicated in the pathogenesis of endometriosis leading to a non-specific inflammatory reaction in the peritoneal cavity.[15] Total Antioxidant Capacity TAC on the other hand, is the ability of serum to suppress the formation of free radicals and to defend cells' structures from deterioration by these radicals. Indeed, it is one of the antioxidant defense mechanism found in the body.[16] While, Glutathione s transferase (GSTs) are proteins with different functions produced by a majority of living organisms that stimulate the conjugation of glutathione (GSH, a tripeptide γ-Glu-Cys-Gly) with variety of toxic substrates provided with an electrophilic center. GSTs, have a major role in eliminating toxic effects of cytotoxic products, (e.g., organic hydroperoxides) released during the process of oxidative stress.[17] In this study levels of adipokines, TNF-α, GST and TAC in patients with endometriosis were measured and compared with the control.

Methodology

This study was conducted at Al-Karkh Maternity Hospital/ Baghdad - Al-Atifiyah for a period from March 20th (2024) to April 20th (2024). The sample of the study included 55 women at reproductive age between (25–40) years old who were suffering from endometriosis in addition to (30) healthy women within the same age group as a control group. The patients were examined clinically by the consultant medical staff. Also, the biochemical laboratory examination and the condition of endometriosis was confirmed by ultrasound examination for each patient. Blood samples were taken from both groups (patients and healthy) and separated using a centrifuge, then the level of their physiological variables were measured.

Estimation of Sex Hormones, Adipokines and Tumor Necrosis Factor

Levels of sex hormones (Testosterone, LH and FSH) were estimated according to the American Accu. Whereas, levels of Leptin, TNF-α, adipisin, Ghrelin were estimated according to the Chinese Bt-laboratory kit. ELISA technique was used for measuring these variables.

Antioxidant Enzyme and Total Antioxidant Capacity TAC

Activity of the GST enzyme was estimated according to the exhaustive method by researcher.[18] Whereas, the level of (TAC) was estimated based on the ferric reducing ability (FRAP) assay as indicated by Benzie.[19] The principle of this method is reduction of the ferric-tripyridyltriazine complex to the ferrous form which leads to the development of an intense blue color. This is in turn can measured spectrophotometrically at a wavelength of (593) nm.

Statistical Analysis

Statistical analysis for data obtained from this study was achieved by using the (SPSS) statistic system and debriefing the arithmetic mean and S.D. The *t*-Test was also applied to find out the differences between the control and patients. Significant differences were chosen for the studied groups at probability ($P \leq 0.05$). Receiver operating characteristic (ROC) another statistical test, was also applied in this study, the area under the curve (AUC) was assessed by MedCalc. V.20 for all parameters in this study. The (AUC) measure of how well variables can distinguish between two diagnostic groups (diseased/normal). The (AUC) score can range (0 to 1).

Results

Table 1 displayed levels of the studied parameters in patients and control group as (mean ± S.D). A significant decrease in levels of testosteronr at ($P < 0.019$) for patients, a significant decreament also was seen in levels of LH, Ghrelin, Glutathion S-transferase (GST) and Total antioxidant Capacity (TAC) at ($P < 0.0001$) for all patients. While a significant elevation was seen in levels of FSH, Leptin, Adipsin and Tumor Necrotic Factor (TNF-α) in all patients at ($P < 0.0001$).

Serum level of testosterone was significantly ($P < 0.019$) lower in patients than in control (0.795 ± 0.438 vs 1.134 ± 0.868). A high significant alterations ($P \leq 0.0001$) were observed in levels of the following parameters in patients compared to control. Leptin was higher (17.241 ± 2.882 vs 8.898 ± 1.126), while, level of Gherlin was lower (4.110 ± 1.624 vs

Table 1. **Levels of (Testosterone, FSH,LH, Leptin, Adipisin & Ghrlin) hormones and (TNF-α, GST, TAC) in the sera of patients and control group**

Groups	Mean ± SD		*P*-value
Parameters	**Control (*n* = 30)**	**Patients (*n* = 55)**	
Testosterone (ng/ml)	1.134 ± 0.868	0.795 ± 0.438	0.019*
FSH (mIU/ml)	9.938 ± 1.495	12.041 ± 1.622	<0.0001*
LH (mIU/ml)	7.649 ± 1.735	2.343 ± 0.825	<0.0001*
Leptin (ng/ml)	8.898 ± 1.126	17.241 ± 2.822	<0.0001*
Adipisin (ng/ml)	1052.155 ± 21.595	2053.829 ± 18.668	<0.0001*
Ghrelin (ng/ml)	8.945 ± 2.137	4.110 ± 1.624	<0.0001*
TNF-α (ng/ml)	61.961 ± 5.117	81.214 ± 5.105	<0.0001*
GST (U/L)	79.914 ± 6.3467	44.070 ± 6.902	<0.0001*
TAC (mIU/ml)	25.468 ± 4.4539	21.668 ± 3.1473	<0.0001*

Mean ± S.D, *significant at (***P ≤ 0.05***).

8.945 ± 2.137). An elevation in levels of adipsin (2053.829 ± 18.668 vs 1052.155 ± 21.595) and TNF-α (81.214 ± 5.105 vs 61.961 ± 5.117) were also observed, Figure 1.

A highly significant alterations ($p \leq 0.0001$) were seen in levels of the following parameters. LH was lower (2.343 ± 0.825 vs 7.649 ± 1.735) but, FSH was higher in patients than control (12.041 ± 1.622 vs 9.938 ± 1.495), Figure 2A. Level of total antioxidant capacity TAC was lower in patients than control (21.668 ± 3.1473 vs 25.468 ± 4.4539), Figure 2B and the same result was seen for glutathione-S transferase GST enzyme (44.070 ± 6.902 vs 79.914 ± 6.3467), Figure 2C.

Area Under the ROC Curve (AUC)

Comparing the results with ROC analysis (Figure 3), evaluation of the studied variables were as the following: Testosterone (AUC = 0.578, $P = 0.288$), FSH (AUC = 0.827, $P < 0.001$), LH (AUC = 0.975, $P < 0.001$), Leptin (AUC = 0.999, $P < 0.001$), Adipsin (AUC = 1.000, $P < 0.001$), Ghrelin(AUC = 0.968, < 0.001), TNF-α (AUC = 0.998, $P < 0.001$), GST(AUC = 1.000, $P < 0.001$) and TAC (AUC = 0.721, $P < 0.001$).

Discussion

Endometriosis is a complicated reproductive disease distinguished by, a chronic process of inflammation that is strongly linked to alteration in sex hormonal-dependent pathways, it involves molecular, biochemical, and cellular alterations (multifactorial in origin). These alterations in turn are interconnected and possibly correlated to responses to external stimuli.[20] Levels of both LH and FSH were significantly high as seen in Figure 2A. The ratio of (LH/ FSH) was reduced in patients with endometriosis (0.194) in comparison to control (0.769) as calculated from Table 1. This was in consistence with Dinsdale[21] who reported that in contrast to PCOS, endometriosis can be characterized overall as involving a reduced LH to FSH ratio. Whilist, Kulinska[22] noted statistically significant higher ratio of LH to FSH concentrations in women with endometriosis compared to intact women. Another study revealed none significant alterations in serum levels of FSH and LH between endometriotic patients and control. But, some FSHR and LHR single nucleotide polymorphisms (SNPs) were observed in those patients.[23] It is well known that FSH play an essential role as coordinator for follicular development and differentiation in the granulosa cells of preovulatory follicles. Whereas, LH catalyze ovulation of preovulatory follicles by stimulation of multiple cellular signaling pathways.[24] The pituitary-ovarian axis is disrupted in patients suffering from endometriosis and thereby the feedback pathways are altered and prevent normal cyclic changes in the ovary leading to an extended follicular phase. In addition to the existence of abnormal patterns of LH secretion.[25]

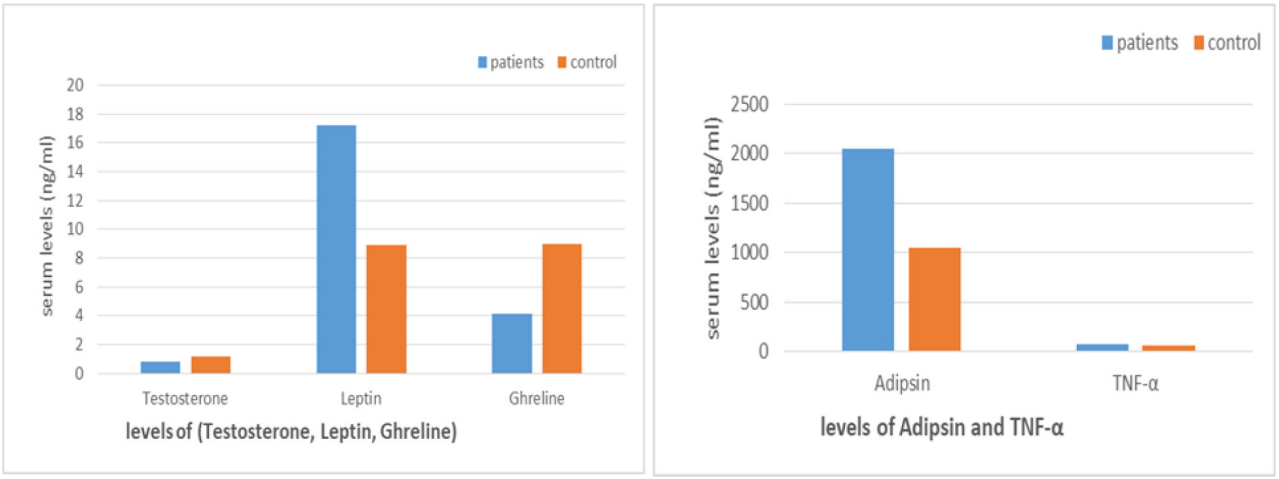

Fig. 1 **Mean levels of (Testosterone, Leptin and Ghreline) on the left and (Adipsin, TNF-α) on the right in patients and control group.**

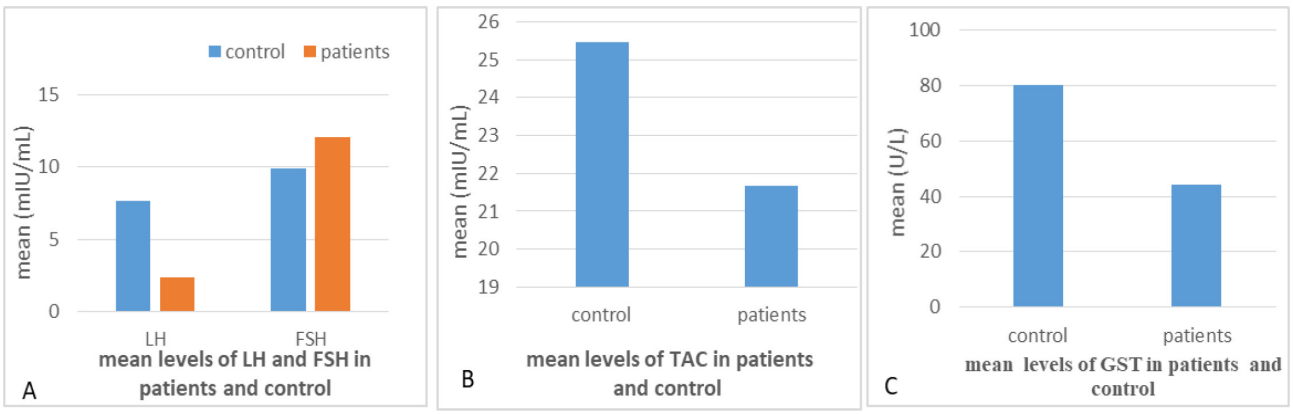

Fig. 2 **A-mean levels of LH and FSH hormones, B-mean levels of TAC, C-mean levels of GST enzyme in patients and control.**

Levels of testosterone were significantly decreased in patients compared to control, Figure 1. This result was in line with Ono[26] who documented that lower levels of serum testosterone is seen in patients with endometriosis than those without and a low serum testosterone may induce the apoptosis of granulosa cells in such patients. The conversion of androstenedione and testosterone produced by theca cells to estrone and estradiol E_2 in granulosa cells is catalyzed by aromatase p450 enzyme which is considered as the main enzyme for estrogen biosynthesis in the ovary.[27] So, the activity of this enzyme is pivotal in the reduction of testosterone levels. Recently, there is an evidence that aromatase p450 is expressed in endometriotic lesions which can then synthesize their own E_2.[28]

Leptin levels were highly significantly ($p < 0.0001$) elevated in patients than in control, Figure 1. This result was in agreement with Hussein[29] who carried out a cross sectional study at Al-Yarmouk Teaching Hospital in Iraq and observed a significant elevation in levels of leptin in the sera of endometriotic patients in comparison to the control. Moreover, Bedaiwy[30] and Matarese[31] observed an increase in leptin levels in the peritoneal fluid (PF) of endometriotic patients compared to healthy women suggesting a pro-inflammatory and neoangiogenic activity of this factor in the pathogenesis of the disease. Interestingly, leptin play a part in controlling gonadotropin secretion by interacting with and stimulating the hypothalamic pituitary ovarian axis (HPO).[32] In human, an anomalous increase in leptin gene expression was detected in ectopic endometriotic tissues. This in turn enhance stromal cell proliferation which may be linked to the pathogenesis of endometriosis.[33] Besides, expression of leptin receptors were detected in endometrial cells. So, human ovarian follicles were assumed to produce leptin which in turn stimulates gonadotrophin releasing hormone (GnRH)-secretion from the hypothalamus.[34] This is might be the key for increased levels of gonadotropins in those patients.

Moreover, an increase in the proliferation of monocytes and induction in the expression of cytokines (TNF-α and IL-6) and surface activation markers is stimulated by leptin. An *in vitro* studies applied on fresh B cells isolated from human subjects, revealed that leptin stimulates the production of TNF-α, IL- 6, and IL- 10.[35] An alteration is observed in levels of inflammatory mediators and growth factors in addition to augmentation in functions of macrophages, lymphocytes and natural killer NK cells in peritoneal fluid of endometriotic patients. In such patients, macrophages are more dominant in the peritoneum and their activity in regulating the events involved in the production of cytokines, prostaglandins, growth factors and complement components is high compared to healthy women.[36] A significant decrease was seen in levels of gherlin, Figure 1. This result was in agreement with Rathore[37] who noticed that median level of ghrelin was reduced but for leptin was elevated in patients with endometriosis versus patients

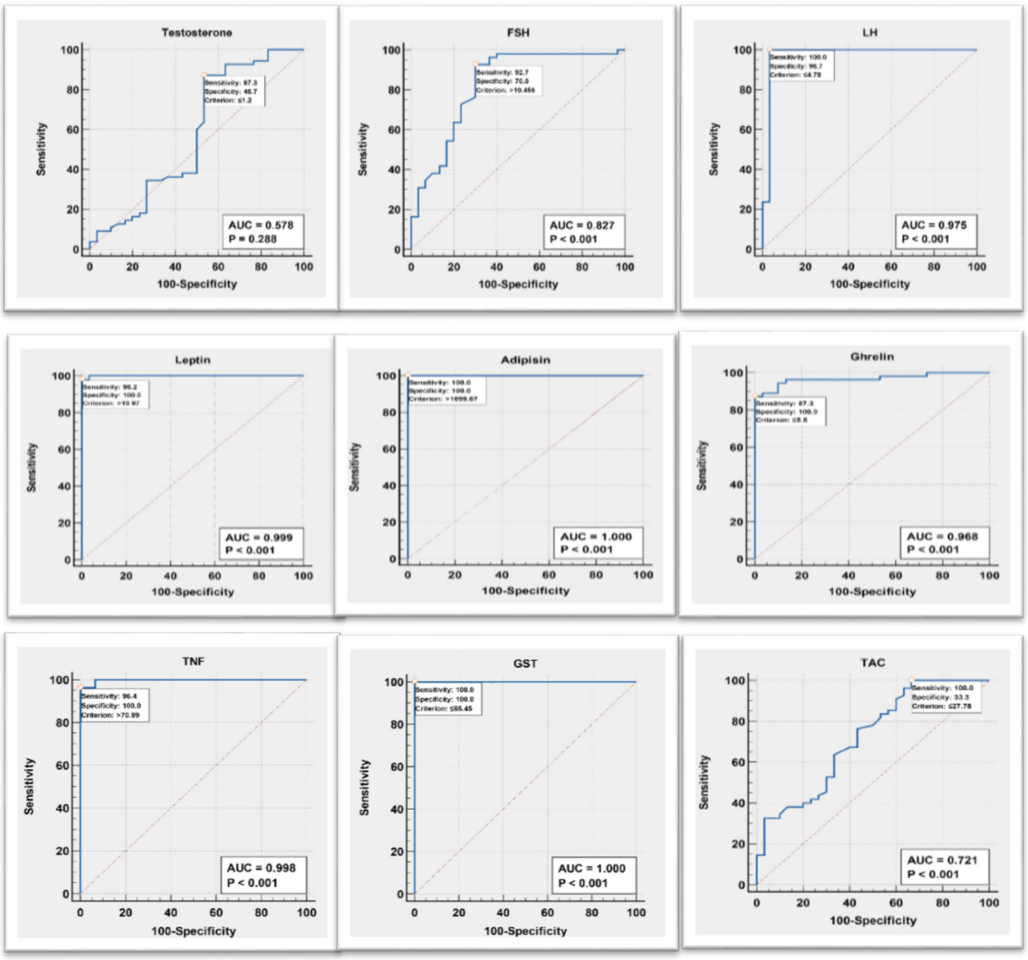

Fig. 3 **Receiver operating characteristic (ROC) curve analysis AUC of (Testosterone, FSH, LH, Leptin, Adipsin, Ghrelin, TNF-α, GST and TAC) in patients and control group.**

with no endometriosis. Moreover, a study conducted by Fernández-Fernández[38] evidenced that gherlin directly catalyst LH secretion by the pituitary in pre-pubertal female rats. These data also reinforce the concept that ghrelin other than GH, control production of pituitary hormones, suggesting the involvement of ovarian signals in the mediatory effects of ghrelin on LH secretion at the pituitary level.

An increase in adipsin levels in patients' sera were seen in Figure 1. In fact adipsin is complement factor D, which has a role in the alternative pathway of complement activation. Both Adipsin and Factor C of the complement are required for the production of C3 a. This factor in turn acts as an anaphylatoxin which stimulates inflammation, chemotaxis, vascular permeability, and leukocyte activation.[35]

Seriously, inflammation possess a vital role in the pathogenesis of endometriosis.[39] TNF-alpha is one of the major cytokines involved in this process. On the other hand, inflammatory cells like neutrophils and macrophages take a part in inflammation, and macrophage in particular, is associated with estrogen.[35] An increase in the activity of macrophages by secreting cytokines (IL-8, IL-10, and TNF-α) is found in peritoneal fluid of endometriotic patients at levels more than those of fertile women. Thus, these cells reflect the degree of endometriosis progression since they can boost and maintain an inflammatory environment.[20] Damaged red blood cells and the apoptotic endometrial cells are factors that activate and trigger mononuclear phagocytes.[40] An increase in the concentration of TNF-α in the peritoneal fluid is highly correlated to endometriosis and high levels of this factor sound to be corresponding to more advanced phase of the disease.[36]

A significant decrease was observed in levels of TAC in sera of patients, Figure 3. This result was partially in agreement with Nassiri[41] who observed a significant lower concentration of TCA in follicular fluid (FF) of women with endometriosis as compared to the control group. Yet, none significant difference was seen in level of this parameter in the sera between both groups. A reduction in antioxidant capacity was also seen in non-fertile women with endometriosis by Prieto.[42] Whereas, our results disagree with Polak[43] who found out a significant high level of total antioxidant status (TAS) in peritoneal fluid (PF) of women with idiopathic infertility but non significant difference was found between endometriotic patients and controls. Whilst, a study by Jelodar and Azimifar[44] involved curcumin effect on a rat model with endometriosis. Results revealed that level of TAC was significantly lower in the sham and endometriotic groups compared to the control group and the lowest level was in the curcumin group. Finally, level of GST in sera of patients was significantly lower than control. Recently, it was demonstrated that levels of GSTT1 in serum and peritoneal fluid of endometriotic patients decreased in comparison to normal control group,[45] which came in line with this study as in Figure 2C. Results of Receiver operating characteristic (ROC) revealed that the sensitivity of LH, TNF-α, GST and adipokines (leptin, adipsin and Gherlin) were equal or closely to (1), Figure 3 which indicates that these parameters were highly correlated to the pathogenesis of the disease and can be dependent as prognostic indicators.

Conclusion

Based on the results obtained from this study and ROC curve analysis, it is concluded that alterations in levels of LH, Gherlin, leptin, adipsin, TNF-α and GST may be taken into account as promising diagnostic markers that reflects the stage of endometriosis resulted from oxidative stress. Identification of these parameters is necessary for early noninvasive diagnosis of endometriosis. A future study with a larger sample and well diagnosed endometriosis according to the stage, is needed to confirm immunological role of (Adipsin and Gherlin) as a prognostic parameters.

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Conflict of Interest

None.

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