Original Article

Effect of Plasma Soluble Urokinase-Type Plasminogen Activator Receptor and Plasminogen Activator Inhibitor-1 Levels in the Plasma of Babylon Women with Breast Cancer

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Abstract

Background: Worldwide, the occurrence of breast cancer is elevated as well as the number of mortality in women cancers. The movement of cancer cells from the first stage and invasion of the surrounding tissue are called cancer metastasis. The fibrinolytic system, in the urokinase-type plasminogen activator system, is disturbed due to breast cancer. **Objective:**The education aim to estimate soluble urokinase-type plasminogen activator receptor (s-uPAR) and plasminogen activator inhibitor-1 (PAI-1) levels in the plasma of Babylon women with breast cancer and control groups. **Materials and Methods:** The case–control group was made up of 42 women (presumably healthy women), whereas the patient group was made up of 42 women with breast cancer .In plasma, the concentrations of s-uPAR and PAI-1 levels were estimated by enzyme-linked immunosorbent assay (ELISA), the statistical analysis was conducted by the SPSS software. **Results:** The result suggests that elevated in PAI-1 and s-uPAR levels, in the patients group compared with the control group ($P < 0.05$). **Conclusion:** The women with breast cancer had elevated serum levels of PAI-1 and s-uPAR. Based on the results of this investigation, this indicate that PAI-1 and s-uPAR act as prognostic indicators in breast cancer women.

Keywords: ELISA, plasminogen activator inhibitor-1, soluble urokinase-type plasminogen activator receptor

Introduction

Breast cancer refers to cancer that starts in the breast, and patients and doctors are worried about the prediction of its survival. Besides, the analytical factors represent the parameters that are related to the consequences of tumors. The main utilized prognostic factors for breast cancer comprise the appearance of patients (age and menstrual state), and structures of the tumor (status of node, stage of TNM and size). Several serum markers could be used for the detection of tumors, yet their role regarding breast cancers is unknown.[1] Besides, there was a positive relation between the tumor and its markers. Still, X-rays in some cases felt to recognize the tumor cell. Moreover, the tumor becomes malignant when cells invade the surrounding tissues or spread to other organs. The exact causes of breast cancer are unknown, but sex hormones of women, family history, and age might be the main causes for the development of the disease.[2]

One member of the serine proteinase inhibitors (serpin) superfamily is PAI-1. About 350–400 amino acid residues are present in each serpin. The "Stressed-to-relaxed" conformational changes have important features for serpin protein family members leading to thermodynamic stabilizations and the inhibitory mechanisms of serpins have been based on such transition. The serpins are divided into two groups,

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inhibitory serpins and noninhibitory serpins. PAI-1 is a member of the inhibitory serpins group, an inhibitor of plasminogen activators.[3] There are two forms of PAI-1, the tissue-type plasminogen activator (t-PA) and the urokinase-type plasminogen activator (u-PA). Additionally, the plasminogen activator inhibitors (PAIs) have the role of blocking the conversion of plasminogen to plasmin. PAI-1 is an inhibitor due to t-PA and u-PA, and manager of the fibrinolytic system.[4]

The movement of cancer cells from the first stage and invasion of the surrounding tissue are called cancer metastasis. This process required the fibrinolytic system, exactly the urokinase-type plasminogen activator system. On tumor cells and monocytes, uPA binds to the urokinase-type plasminogen activator receptor (uPAR), helping the transformation of plasminogen to plasmin.[5] The mechanism for the degradation of extra-cellular matrix directly or indirectly by plasmin includes the activation of matrix metalloproteinases, which destroy collagen and other matrix proteins, thus permitting the invasion of the extracellular matrix and the surrounding tissues by tumor cells and monocytes. PAI-1 and PAI-2 inhibited the activity of uPA and uPAR. Plasmin is inhibited by the formation of plasmin–2-antiplasmin complexes. Elevated levels of uPA, uPAR, and PAI-1 are linked with the poor prediction of cancers, such as lung, stomach, bladder, ovarian, and breast cancers.[6]

Predominantly, uPAR levels in tissue and cytosol have been considered. Plasma levels of soluble uPAR (s-uPAR) reveal local expression and release of uPAR. Accordingly, in patients with cancer, the plasma levels of s-uPAR might be an indicator for uPAR expression on tumor cells or monocytes, in metastasis breast cancer plasma levels of s-uPAR are elevated significantly.[7] In breast cancer patients, it has been revealed that higher levels of s-uPAR are linked with poor diagnosis, independent of the status of lymph nodes, tumor size, and estrogen receptor.[8]

Materials and Methods

The current study involved 42 women (diagnosed with breast cancer) from Al-Hillah. Aged between 35 and 65 years, the samples of patients were taken when coming to hospitals for checking and treatment, during the period from December 1/12/2023 to April 30/4/2023. Patients and women were separated into two stages and grades (II and IV), also into three subgroups according to ages (35–45), (45–55), and (55–65) years, and three subdivisions rendering to body mass index (BMI, kg/m^2) (normal weight and overweight). The control group was composed of 42 women who appeared as healthy aged between 36 and 64 years. The ages were matched for healthy and patient groups. Mean ± SD was used for the expression of data. Student *t* test and the linear regression analysis were used for the analysis of data. The result stated an odd ratio, 95% confidence interval, and *P* value. The SPSS (version 20) software package was used for statistical analyses. *P* value of <0.05 was considered significant.

Ethical approval

Before collecting samples for the study, the acceptance from the scientific committee in the Biochemistry Department of Babylon Medical College was taken. All the participants in the present study have an explanation of the aims and techniques to gain verbal approval.

Results

In the present study, 42 women diagnosed with breast cancer were enrolled as the study group. The levels of s-uPAR and PAI-1were increased significantly in the patient group compared with the control group, as shown in [Table 1].

The correlation (r) between the measured parameters and variables is shown in [Table 2]. The results of the comparison between plasminogen activator inhibitor-1 levels according to BMI and age in women with breast cancer disease are shown in Table 3 and 4.

Table 1: Biochemical characteristics of the control and patient groups

Variables	Group	No	Mean ± SD	95% confidence interval for Mean		Sig. *P* value
				Min	Max	
s-uPAR (pg/mL)	II	22	185±2.3	182.4	185.3	<0.05
	IV	20	194.2±4.4	190.4	199.2	
	Control	42	170±9.7	160.3	180.7	
PAI-1 (U/mL)	II	22	10.8±0.5	10.3	11.2	0.05
	IV	20	12.2±0.2	12	12.4	
	Control	42	9.9±2.3	7.4	12.2	

significant = *P* < 0.05

Table 2: Correlation (*r*) between the measured parameters variables against each other

Sequence	Variables against each other	Correlation (*r*)	Sig. *P* value
II		0.72	<0.05
IV	s-uPAR versus PAI-1	0.29	>0.05

Table 3: Serum PAI-1level at different ages

Age (years)	s-uPAR	PAI-1	*P* value
35–45	187.9±0.2	10.5±0.03	<0.05
45–55	195.3±0.05	11.9±0.07	<0.05
55–65	189.7±0.4	11.15±0.1	<0.05

Table 4: Comparison between plasminogen activator inhibitor-1 levels according to BMI in women with breast cancer disease

BMI	s-uPAR	PAI-1	*P* value
Normal weight	186.5±0.9	19.8±0.04	<0.05
Overweight	192.7±0.4	12.1±0.02	<0.05

Discussion

Plasminogen is converted into plasmin by the PA system, these processes are important in physiological roles. As well, it is important in cancer invasion and metastasis by allowing the cancerous cells to invade the tumor site and spread to other sites.[9]

Elevated plasma levels of PAI-1 might be attributed to hypercoagulation, which means higher expression of PAI-1 in adipose tissue due to exposure to high-energy diets, grafted fat via itself has no capacity for motivating the cellular proliferations in breast cancer, chronic inflammation, and/or higher levels of PAI-1. The severity and negative outcomes were shown in many diseases caused by elevated plasma levels of PAI-1 antigen and its activity.[10] These findings showed that PAI-1 might be used as a biomarker and possible therapeutic target. The uPA, PAI-1, and uPA receptor (uPAR) are the plasminogen-activating proteins, these proteins might be used as tumor markers. Typically, the elevated uPAR, PAI-1, and uPA levels in the tumor tissues are indicators of bad prognosis in several kinds of human cancers, like renal, lung, breast, ovarian, stomach, breast, endometrial, and colon cancers.[11] As the ductal carcinoma in situ is suggestive of injury in the basement membrane and myoepithelial layer that is, essential for expressed PAI-1, which is mediated by cytokines and/or changes in the adhesion molecules, which are expressed and interact with stroma.[12]

This study revealed a significant difference in PAI-1 ($P < 0.05$) between patients and control groups is shown in Table 1. This finding agrees with a previous study by Croucher *et al.*[13] showed that PAI-1 overexpressed in invasive ductal carcinoma than lobular carcinoma as a result of overexpression of human epidermal growth factor receptor 2 (HER2) negative in the invasive ductal carcinoma and PAI-1 positively correlated with HER2/ negative level.

Another study showed a higher level of PAI-1 and low activity of TFPI in patients with invasive ductal carcinoma compared with invasive lobular cancer patients, these results suggested that the fluctuations in hemostatic profile related to the histology of breast cancer.[14]

In this study, significant variance in receptor (uPAR; $P < 0.05$) among patients and control groups was demonstrated is shown in Table 1. This finding agreement with a prior study conducted by Sereff *et al.*[15] showed that uPA concentration elevated in breast carcinomas and these elevations related to the progression of the disease, and lead to a low survival rate

This study, Table 2 shows a positive correlation between PAI-1 and uPAR at stage II, whereas no correlation in stage IV. These results are acceptable with the results of another study,[16] which showed elevated levels of PAI-1 correlated positively with stages of disease, elevated levels of PAI-1 correlated with the progression of tumors and lymph node status, therefore, PAI-1 might be a marker for cancers development. This finding agrees with a previous study by Deryugina *et al.*[17] confirmed that the higher level of s-uPAR in metastatic breast cancer patients compared with nonmetastatic patients and healthy controls.

Table 3 explains that PAI-1 levels elevated at 35–45 years and 45–55 years when compared with 55–65 years. These results agree with the study of Stillfried *et al.*[18] indicated that associations between PAI-1 and age, and elevated PAI-1 in postmenopausal women. A prior study by Andres *et al.*[16] observed an alteration of PAI-1 level in the menstrual cycle in patients with premenopause cancer. PAI-1 was pathologically elevated in the patients with post-menopause cancer; however, this increase did not associated with the metastatic sites or the metastatic location.

In patients suffering from obesity and/or breast cancer, PAI-1 is the protein located in high concentrations in the adipose tissues; therefore, it might be used as a marker. Several studies support such findings in contrast to a study conducted by Carter *et al.*[19] observed no differences in PAI-1 levels in several tumor grades. In the present study, there has not been a significant difference in the levels related to PAI-1 in breast cancer women

according to their BMI, as in Table 4. In contrast to other studies by Davoodi *et al.*[20] reported that elevated production of PAI-1 levels in adipose tissue, higher levels of PAI-1 in obesity might promote the vascularization and invasiveness of tumors because of obesity lead to increasing inflammatory cytokines, which elevated the levels of PAI-1.[21-24]

Conclusion

This study revealed significant differences in PAI-1 and s-uPAR levels between the carcinoma and control group. Besides, variables, such as age, stage, and BMI, in breast cancer women affected the level of PAI-1 and s-uPAR, which indicates the role of PAI-1 and s-uPAR as a predictive marker in breast cancer women.

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Conflicts of interest

There are no conflicts of interest.

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