Article

A correlation study of paraoxonase-1 and GSH with renal function in Iraqi gynecological cancer.

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Abstract

Paraoxonase (PON 1) is an important antioxidant enzyme that hydrolyzes lipid peroxides and acts as a biomarker for carcinogenicity. The aim of this study was to compare the serum levels of paraoxonase-1 activity and glutathion GSH in Iraqi female cancer patients to those in healthy controls. Serum paraoxonase-1 activity and GSH levels were measured in patients with ovarian cancer (n = 40), uterine cancer (n = 40), and controls (n = 40). Results: Patients exhibited significantly decreased serum paraoxonase and GSH levels compared to controls ($p < 0.001$).Conclusion: Low blood PON 1 activity may lead to an impaired antioxidant defense system, which is significant in carcinogenesis in people with gynecological malignancies.

Keywords :Gynecological Cancer, , paraoxonase-1 and GSH

Introduction

Gynecological malignancies are among the most frequent cancers in women, making them crucial for public health[1]. Ovarian cancer malignancy is the most widely recognized reason for mortality globally and ovarian cancer is one of gynecologic malignancy that ranks third after severical and uterine cancer in the world for women [2-4].There are 95% of Ovarian are due to epithelial ovarian cancer while 5% of Ovarian cancer are due to non-epithelial type of Ovarian cells including small cell carcinoma, ovarian sarcoma[5]. Uterine Cancer: Uterine

malignancy is one of the highest-level of tumors in women reported from world wide[6] . Endometrial malignancy emerges from the in-ward layer endometrial of the Uterus that leads to 90% of uterine disease followed by uterine sarcoma that emerges from the external layer (myometrium) 8%[7, 8].It is the most often identified gynecological danger in women[9]. The antioxidant paraoxonas-1 (PON1) belongs to the calcium-dependent hydrolase family and has a variety of enzymatic activities such as lactonase, arylesterase, peroxidase, and phospholipase. It is recognized as both an antioxidant enzyme that inhibits LDL oxidation and an anti-inflammatory enzyme that reduces the synthesis of proinflammatory mediators[10-12]. The activity of this enzyme is affected by oxidative stress [13]. It has been linked to the etiology of several inflammatory diseases, including atherosclerosis, diabetes, and cancer [14, 15]. Tripeptide glutathione (GSH) is the most common low-molecular-weight, water-soluble antioxidant. GSH's involvement extends beyond the management and maintenance of redox equilibrium in cells to include antioxidant protection, thiol-disulfide exchange of peptides and proteins, and redox-dependent control of cell signaling and gene expression. Protein catabolism causes the release of adiposable nitrogen molecules in the form of ammonia, which is subsequently converted to urea in the liver via the urea cycle[19]. A complete urea cycle transforms two molecules of nitrogen into one molecule of urea [20]. Serum creatinine and urea are routinely used indicators to estimate renal function. Creatinine is mostly released by muscle tissue. [21]

Materials & methods

Blood samples about 5 mL were collected from 80 Gynecological cancer: (40 female patients with ovary cancer and 40 females with uterine cancer) and 40 healthy controls who were from patients related. All groups patients and control in the same age: (40-60) years. Also, patients with Gynecologic cancer were enrolled at oncology teaching hospital in medical city in Baghdad for duration time October 2022 to April 2023. Paraoxonase-1(PON-1) and Glutathione (GSH) were estimated by Kit ELISA (,GHSHu , PON1Hu) from could-clone chain respectively.

Statistical evaluation

The investigation's findings were displayed as mean±SD. To compare the patient and control groups, a t-test was run. Significant P values of(≤ 0.05) were significant were also discovered[22]

Results and discussion

Table 1 displays the biochemical features of the sample population sera of Iraqi Gynecologic female cancer patients with ovarian cancer (G1), uterine cancer (G2) and healthy controls (G3).

Table (1) concentration (mean ±SD) of paraoxonase-1 (PON-1), GSH, Urea and Creatinine in Gynecologic female cancer and Iraqi healthy control.

Parameters	Gynecologic cancerMean ± SD		Health control G3 n=40 Mean ± SD	*P-value*		
	Ovary cancerG1 n=40	Uterine Cancer G2 n=.40		G1& G2	G1& G3	G2 & G3
PON-1(U/ml)	133.9± 31.85	138.5± 33.07	345.2±92.82	<0.001	<0.001	<0.001
GSH (U/ml)	61.45± 11.08	58.9±9.8	76.76±1.15	<0.001	<0.001	<0.001
Urea (U/ml)	32.5 ± 8.7	30.44± 6.7	24.18±3.19	<0.001	<0.001	<0.001
creatinine (U/ml)	1.15±0.013	0.95± 0.026	0.49±0.013	<0.001	<0.001	<0.001

**P-value*< 0.001 significant

The recent study in Table (1) showed the levels of paraoxonas-1 (PON-1), Glutathione (GSH) and Kidney function (Urea and creatinine) in Three groups: G1: Gynecologic cancer (Ovary), G2: Gynecologic cancer (Uterine) and G3: healthy control.

The results in that table showed a high significant reduction in PON-1 activity in Iraqi females with ovarian cancer when compared to Uterine cancer and healthy controls, as well as a high significant decline in Uterine cancer when compared to healthy controls. Cancer is a disease defined by cellular mutation, proliferation, and abnormal cell growth. It is sometimes separated into three stages: commencement, promotion, and advancement, each of which involves oxidative stress [23].

The initial stage of cancer start is defined as a stable, heritable alteration. Initiating agents produce genetic alterations such as mutations, DNA damage, and structural changes [24].The second stage of carcinogenesis, promotion, is triggered by either

endogenous or exogenous cell growth stimulation. In this stage, reactive oxygen species (ROS) can alter gene expression and induce modification of the second messenger systems, increasing cell proliferation or inhibiting apoptosis and clonal expansion of initiated cells to produce a preneoplastic lesion, whereas in the third stage (progression), benign preneoplastic lesions are converted into neoplastic cancer[25]. The importance of antioxidants in connecting chronic inflammation and cancer via preventative mechanisms based on enzymatic and non-enzymatic antioxidant molecules [26, 27].

The enzymatic antioxidant paraoxonase-1 (PON1) has generated great attention since it is the protein responsible for the majority of high-density lipoprotein's antioxidant properties[28]. So, a significantly lower amount of PON-1 in gynecological cancer may be to prevent PON-1 from creating oxidized low-density lipoprotein and inactivating LDL-derived oxidized phospholipids once formed, as well as PON-1 from oxidizing phospholipids in HDL[29]. In contrast, PON-1 scavenges carcinogenic lipid-soluble radicals [30]. Lowering the level of (PON-1) in gynecologic cancer helps to maintain the balance of antioxidant cancer development [25]. As a result, reducing PON-1 levels protect against oxidative stress by hydrolyzing active oxidized phospholipids, destringing lipid hydroperoxides and H2O2, and detoxifying homocysteine[31]. Also, the levelsof (PON-1) was lower in ovary cancer than in uterine cancer, indicating that Furthermore, the level of (PON-1) was greater in ovary cancer than in uterine cancer, suggesting that PON-1 genetic variations may influence the risk of epithelialovarian cancer in women[32]. Another antioxidant, GSH, was shown in Table 1 to be considerably lower in gynecological cancer (ovarian and uterine cancer) than in a healthy reference. Lowering the level of (PON-1) in gynecologic cancer helps to maintain the balance of antioxidant cancer development [25]. As a result, reducing PON-1 levels protect against oxidative stress by hydrolyzing active oxidized phospholipids, destringing lipid hydroperoxides and H2O2, and detoxifying homocysteine[31]. PON-1 genetic variations may influence the risk of epithelialovarian cancer in women[32]. Cisplatin's anticancer effect has previously been attributed to its ability to bind nucleus DNA adducts, which disrupt transcription and replication processes and cause widespread cell death[36]. Nowadays, this view appears to be an oversimplification, given that only a few intracellular cisplatin interacts with nuclear DNA, and cisplatin has cytotoxic

effects even in enucleated cells, implying that cisplatin exerts cytoplasmic toxicity by binding to various [37] intercellular molecules, with reduced glutathione GSH being its primary target [38].The binding of cisplatin to GSH disrupts the redox equilibrium, resulting in the accumulation of reactive oxygen species (ROS), which can directly induce apoptosis by opening the mitochondrial permeability transition hole. So, cancer cells produced more ROS because of mitochondrial dye function, altered metabolism, and frequent genetic mutations, so they boosted antioxidant (GSH) levels to maintain balance[39]. The current study (Table 1) also found levels of renal function (urea and creatinine) in gynecologic cancer and healthy control. Furthermore, the results in that Table showed that gynecological cancer groups had considerably greater levels of urea and creatine than healthy control groups, although these levels were abnormal. Protein breakdown releases disposable nitrogen molecules, including ammonia, a very hazardous toxin [20, 40]. In normally functioning organisms, the detection of ammonia initiates certain mechanisms for disposing of the excess metabolite. The urea cycle converts ammonia to urea, a hydrosoluble, non-toxic metabolite excreted by urine[41]. Creatinine serum is the most sensitive indicator of renal function since it is constantly generated by the body. Renal impairment [42] causes an increase in creatinine serum, although this study found a normal distribution of this amount after chemotherapy.

Recent data find that chemotherapy drug platinum complex doesn't affect on urea and creatinine in gynecologic cancer.

Correlation Analysis

Data in Table 2 and 3 showed correlation study between (PON-1) and (GSH, Urea and Creatinine) in cancer and Uterine cancer respectively.

Table 2 Correlation study of PON-1 with GSH, Urea and Creatinine in Ovary cancer.

	Factors	**GSH**(U/ml)	**Urea**(U/ml)	**Creatinine**(U/ml)
PON-1(U/ml)	**R** person	**0.24**	**0.034**	**0.741**
	P	**0.923**	**0.88**	**0.000**

Table 3 Correlation study of PON-1 with GSH, Urea and creatinine in Uterine cancer.

PON-1(U/ml)	Factors	GSH(U/ml)	Urea(U/ml)	Creatinine(U/ml)
	R person	0.143	0.326	-0.146
	P	0.58	0.202	0.57

Data in Table 2 showed a high significant positive correlation (+ve) between PON-1 with Creatinine as shown in Figure 1 and no-significant positive correlation with GSH and Urea in ovary cancer.

In uterine cancer also there was a not-significant correlation between PON-1 and all parameters in uterine cancer.

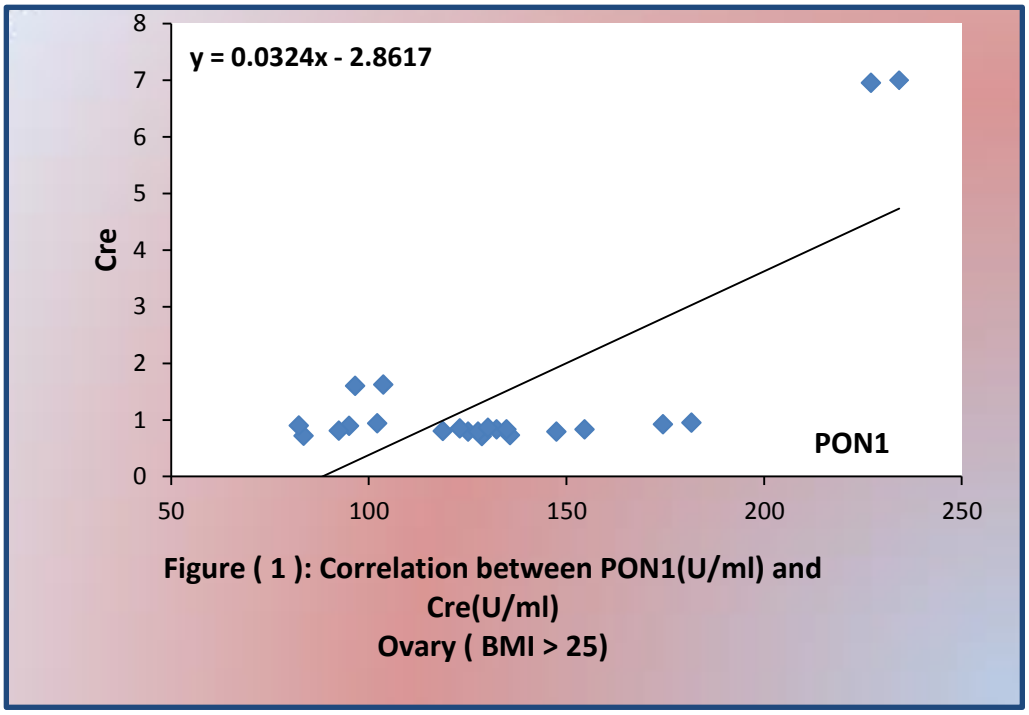

Figure (1): Correlation between PON1(U/ml) and Cre(U/ml) Ovary (BMI > 25)

Conclusion

Paraoxonase-1 enzyme plays an important role as antioxidant enzyme for patients with gynecologic cancer and its could be a good marker for cancer disease

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