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CORRELATION STUDY OF OBESTATIN AND PROGRANULIN WITH LIVER FUNCTION ENZYME IN IRAQI FEMALES PATIENTS WITH COLORECTAL CANCER

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Abstract

The second most commonly diagnosed cancer is colorectal cancer (CRC) is in female. The levels of progranulin, obestatin and liver enzymes including ALT, AST and ALP were measured in forty five sera in female patients suffering from CRC before chemotherapy initiation treatment as G1, G2 after first chemotherapy cycle and G3 after second chemotherapy cycle compared with thirty female as a healthy control G4. Results showed a high significant increased in progranulin concentration and a high significant decrease in obestatin in G2 than other groups.

The correlation between progranulin and ALP was a significant negative (-ve) relation while obestatin with AST gave a significant positive (+ve) correlation in G. The results also showed non significant negative (-ve) and positive (+ve) between progranulin, obestatin with ALP, AST and ALT in other groups.

Key wards: Colorectal cancer (CRC), progranulin, obestatin, liver functions enzyme.

Introduction

The third most common cancer worldwide is colorectal cancer (CRC) in male and female and the second largest cause of death related to cancer (Juan, *et al*, 2017). The CRC developing increases with risk factors such as bad nutritional habits, sedentarism, obesity, intestinal inflammatory disease, polyps, smoking, genetic factors and age (Hamidreza *et al.*, 2017). More than 90% of diagnosed patients are over 50 years old. The incidence of CRC in both gender but it was higher ratio in male than in female (Ferlay *et al.*, 2013).

Progranulin (PGRN) is a glycoprotein, consists of 593 amino acids residues with molecular weight approximately 75-80 kDa (Li *et al.*, 2011). PGRN is known as granulin-epithelin precursor (GEP), proepithelin and GP88/PC-cell-derived growth factor (PCDGF) (Tangkeangsirisin *et al.*, 2004). Numerous tissues secreted PGRN and variety of cells expressed it, which including epithelial cells, haematopoietic cells, neurons, macrophages (Okura *et al.*, 2010), skeletal muscle cells, endothelial cells (Toh *et al.*, 2013) and adipocytes (Matsubara *et al.*, 2012). PGRN has multifunctional properties including biological and pathological processes, such as embryogenesis (Desmarais *et al.*, 2008), cell growth, tumorigenesis (Ong *et al.*, 2003), wound cure (He *et al.*, 2003), immunity, infection, inflammation (Jian *et al.*, 2012), diabetes (Nicoletto *et al.*, 2015) and insulin resistance(Matsubara *et al.*, 2012). Over expression of PGRN was associated with many cancer types onset (Dong *et al.*, 2016; Li *et al.*, 2012; Alvaro, 2012).

Obestatin is a peptide hormone composed of 23 amino acid derived from ghrelin precursor protein (Elaine *et al.*, 2016). Obestatin has shown many physiological functions and in numerous diseases, including cancer especially gastric neuroendocrine tumors (Volante *et al.*, 2009; Tsolakis *et al.*, 2009).

Liver enzymes involved of alanine aminotransferase (ALT), alkaline phosphatase (ALP) and aspartate aminotransferase (AST). The two aminotransferases (ALT and AST) are used in diagnosis and management because of these enzymes is widely distributed in body tissues but ALT is present in only small amounts, except in the liver (Thapa *et al*,, 2007). Both enzymes may be

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Table 1: Concentrations of PGRN and some biochemical parameters in the serum of female patients and control groups.

P value						Control group (No. 30)	Patients group (No. 45)			Parameters
G3 vs. G4	G2 vs. G4	G2 vs. G3	G1 vs. G4	G1 vs. G3	G1 vs. G2	G4	G3	G2	G1	
0.491 Ns	0.000 h s	0.000 h s	0.418 Ns	0682 Ns	0.000 h s	222.03 ± 81.4101	210.31 ± 38.4549	368.57 ± 63.4296	207.76 ± 27.5375	PGRN (pg/ml)
0.055 Ns	0.000 h s	0.000 h s	0.613 Ns	0.000 h s	0.000 h s	2.17 ± 0.3228	2.42 ± 0.3787	1.57 ± 0.3968	2.13 ± 0.1853	Obestatin (pg/ml)
0.000 h s	0.000 h s	0.000 h s	0.000 h s	0.000 h s	0.000 h s	25.0 ± 0.8402	43.4 ± 2.9104	7.6 ± 0.2910	2.8 ± 0.2169	ALT (U/L)
0.000 h s	0.000 h s	0.000 h s	0.000 h s	0.000 h s	0.000 h s	23.0 ± 0.9075	7.56 ± 1.0761	11.58 ± 1.1038	6.69 ± 1.0808	AST (U/L)
0.000 h s	0.000 h s	0.000 h s	0.000 h s	0.076 Ns	0.000 h s	85.0 ± 0.7670	31.73 ± 1.929	55.49 ± 15.1065	33.99 ± 11.0974	ALP (U/L)

S = Significant, Ns = Non significanth, s = high significant
G1 = patients group before initiation chemotherapy, G2 = patients group after taking first cycle chemotherapy
G3 = patients group after taking second cycle chemotherapy, G4 = healthy control.

elevated in patients presenting with chronic hepatitis, acute viral hepatitis, alcoholic hepatitis, cirrhosis and toxic ischemic injury (Clementine *et al.*, 2010).

Alkaline phosphatase (ALP) is a nonspecific enzyme, mainly produced by liver, osteoblasts of bone and lesser in leukocyte, intestines, kidney and placenta. ALP is localized in the cell membranes and associated with transport mechanisms in liver, intestinal mucosa and kidney. Increasing levels of ALP is associated with many diseases, such as infiltrative liver disease, hepatitis, intrahepatic cholestasis and extrahepatic bile obstruction (Saif *et al.*, 2005). Levels of usually ALP are elevated with metastatic CRC patients.

Materials and Methods

Patient study

The serum of (45) females patients suffering from colorectal cancer with age range between (40-60) years old were enrolled in this study from Oncology Teaching Hospital in Medical City in Baghdad for duration time October, 2018 to October, 2019. The patient's sera were divided into three groups as following:

G1: The colorectal cancer female patients (45) before initiation chemotherapy.

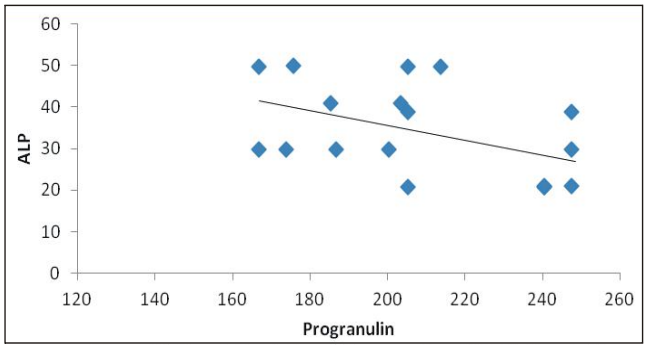

Fig. 1: Correlation between Progranulin and ALP in female G1.

G2: The same patients in G1 after three weeks of first cycle chemotherapy.

G3: The same patients in G1 and G2 after three weeks of second cycle chemotherapy.

The healthy control consist of (30 female) with the same age of patients considered as (G4).

Progranulin, obestatine estimated by ELISA kit No. E-EL-H1578 and E-EL-H1989 respectively. Liver function enzymes ALT, AST and ALP determined by colorimetric methods kits.

Statistical Analysis

The statistical analysis determined by SPSS version (prism ® 7 and Microsoft excel 2013) with significant difference it be equal or below 0.05 (Elliott *et al.*, 2007).

Results and Discussion

The results of this study were listed in table 1. Progranulin (PGRN), obestatin and liver function enzymes (ALT, AST and ALP) in Iraqi female patients with CRC before initiation of chemotherapy, after first and second cycle chemotherapy. The same parameters were measured for the control female group.

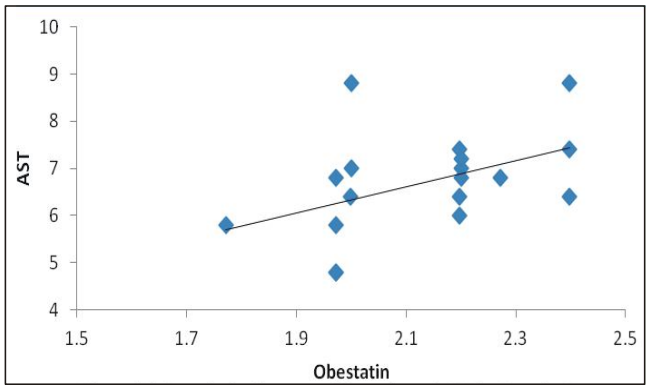

Fig. 2: Correlation between Obestatin and AST in female G1.

Table 2: The correlations between PGRN and some biochemical parameters in sera of CRC patients female before initiation of chemotherapy.

Obestatin	ALP	AST	ALT	Parameters	
-0.003	-0.475	-0.02	0.36	R	PGRN
0.989Ns	0.046 S	0.937Ns	0.142Ns	P	
	0.059	0.458	0.125	R	Obestatin
	0.816Ns	0.056S	0.622 Ns	P	
S = Significant, Ns = Non significanth, s = high significant					

PGRN concentration showed a non significant decreased in G1 *P*= 0.4 with compared healthy control and a high significant increased after the first taking chemotherapy dose G2 *P*= 0.000 than G1, G3 and G4.

PGRN complicated with many processes like inflammation, wound cure, tumoigenesis and the expression status of PGRN in CRC (Yang *et al.*, 2015; Li *et al.*, 2011).

It was found that PGRN acts an important role in CRC fibroblasts activation and induced Ki67 and smooth muscle actin-α in patients' tissues with CRC (Linlin *et al.*, 2017). The increasing level of PGRN in G2 after first cycle of chemotherapy which due to highly expressed in CRC, promoted proliferation and angiogenesis through tumor necroses factor and due to extracellular regulated kinase (Yang *et al.*, 2015).

A high significant decreased in obestatin levels in (G2) than other groups. Obestatin pathway shows antioxidant and anti-inflammatory effects in many organs in the human body (Scrima *et al.*, 2007).

The biological effect of obestatin shows by binding to G protein-coupled receptor 39 (GPR39) (Scrima *et al.*, 2007). So that obestatin by its name will inhibits food intake and by the stomach secreted mainly and also observed in other gastrointestinal organ. Previous study showed that squamus cell carcinoma was positive for obestatin and the lowering of it due to the treatment by chemotherapy dose which effecting on the obestatin in squamous cell carcinoma (Zhang *et al.*, 2008).

In addition table 1, shows a low levels of ALT, AST and ALP in G1 than other groups and the liver function enzymes were independent prognostic factor for colorectal cancer (Alnema *et al.*, 2010). Metastatic for those patients with normal value of that enzymes, except GPT which is increasing after taking second chemotherapy dose (G3) which is taking 5-Fluorodeoxy uridine (5FUDR) and 5-Fluro uracil (5-FU) for therapy so the abnormal (increasing of GPT) may due to the toxicity of drug (5FUDR) and (5-FU) (Chang *et al.*, 1987; Hohn *et al.*, 1989).

Table 3: The correlations between progranulin and some biochemical parameters in sera of CRC patients females after first cycle of chemotherapy.

Obestatin	ALP	AST	ALT	Parameters	
-0.312	0.260	0.246	0.201	R	PGRN
0.138Ns	0.298 Ns	0.325Ns	0.423Ns	P	
	-0.316	0.171	-0.219	R	Obestatin
	0.202Ns	0.498Ns	0.382 Ns	P	
S = Significant, Ns = Non significanth, s = high significant					

Table 4: The correlations between progranulin and some biochemical parameters in sera of CRC patients female after second cycle of chemotherapy.

Obestatin	ALP	AST	ALT	Parameters	
-0.228	-0.416	-0.189	-0.065	R	PGRN
0.285Ns	0.086 Ns	0.454Ns	0.799Ns	P	
	0.123	0.295	0.229	R	Obestatin
	0.627Ns	0.235Ns	0.360 Ns	P	
S = Significant, Ns = Non significanth, s = high significant					

The correlations between PGRN with obestatin, ALT, AST and ALP was listed in the table 2.

Table 2, showed correlation data which gave a non significant negative correlation (-ve) between PGRN and (obestatin and AST) and a non significant positive correlation (+ve) with ALT. PGRN gave a significant negative correlation (-ve) with ALP as in fig. 1 and there was a significant positive (+ve) correlation between obestatin and AST in fig. 2 and non significant positive (+ve) correlation with ALT and ALP in female patients before taking chemotherapy dose (G1).

While the correlation in the females patients after first cycle of chemotherapy gave a non significant positive (+ve) correlation between PGRN and (ALT, AST and ALP) and non significant negative (-ve) correlation with obestatin as listed in table 3.

The correlation between obestatin and AST was non significant positive (+ve) and non significant negative (-ve) correlation between obestatin and (ALT and ALP) in female patients after first cycle of chemotherapy.

Table 4, showed a non significant negative correlation (-ve) between progranulin and (ALT, AST, ALP and obestatin) and non significant positive (+ve) correlation between obestatin and (ALT, AST and ALP) in female patient after second cycle of chemotherapy.

Conclusion

This study was the first determined the correlation between progranulin and obestatin in Iraqi female patients with CRC after and before chemotherapy (first and second cycles). It was concluded that PGRN and obestatin may be a good marker to diagnosis of cancer after chemotherapy treatment.

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