Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2015, 4 (2): 557-563

(International Peer Reviewed Journal)

Relationship of Gamma-Glutamyltransferase Activity, Glutathione And Some Electrolytes In Serum Heart Failure Patients

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Accepted on 28th February 2015

ABSTRACT

Gamma-glutamyltransferase (GGT) has been found to be involved in the pathogenesis of cardiovascular diseases, especially coronary artery disease, and the prognosis of cardiovascular disease may be predicted by increasing GGT levels. GGT levels are related to cardiovascular emergencies of chronic heart failure. Gamma-glutamyltransferase(GGT), an important enzyme in glutathione (GSH) metabolism. So studies are made on the relationship between Gamma-glutamyltransferase (GGT) activity, serum reduced Glutathione and some electrolytes such as Na, K, and Cl, in patients with heart failure. We selected 80 patients with heart failure who attended for treatment in Baghdad Medical City, the patients characterized in Electromyo Cardio Gram (ECG) by medical in hospital ,the patient samples were divided into the following(40) females ,(40) males with age ranges from(30-87) year, and(80) normal healthy controls, (40) males ,(40) females with age ranges from 27-79 year.

Keywords: Gamma-glutamyltransferase (GGT), Glutathione (GSH), Coronary Artery Disease (CAD), Systolic Blood Pressure(SBP) and Diastolic Blood Pressure (DBP).

INTRODUCTION

Cardiovascular diseases are threatening human health with rising morbidity and mortality rates. Gamma-glutamyl transferase (GGT) has been found to be involved in the pathogenesis of cardiovascular diseases, especially coronary artery disease and the prognosis of cardiovascular disease may be predicted by increasing GGT levels. GGT levels are related to cardiovascular emergencies of chronic heart failure [1]. GGT is an important enzyme in glutathione (GSH) metabolism, GGT has shown to be involved in the development of cardiovascular disease. The progress and prognosis of cardiovascular disease may be predicted by increasing GGT levels, a tool preferable to other biochemical indicators such as analysis of blood lipid levels. Serum GGT levels have been shown to be an independent predictor of diabetes, hypertension, the metabolic syndrome and coronary artery disease (CAD)[2].

Biocharacteristics of GGT: GGT is a glycosylated protein that is partially embedded in the outer surface of the plasma membrane , the quantitative analysis of serum GGT fractions. Study, four GGT fractions: big-GGT, medium-GGT, small-GGT and free-GGT fractions of different molecular weight (molecular masses >2000 kDa, 940 kDa, 140 kDa and 70 kDa, respectively) were detected by a procedure based on

gel filtration chromatography, followed by post column injection of a fluorescent GGT substrate. Comparatively, GGT activity was decided primarily by the free-GGT and small-GGT fractions. GGT catalyzes the transfer of the gamma-glutamyl moiety from GSH or GSH conjugated to acceptors such as amino acids, di peptides and molecules with similar traits. GGT can provide cysteine, the rate-limiting amino acid, for GSH de novo synthesis by breaking down extracellular GSH into its constitutive amino acids. It is a vital step in maintaining in vivo homeostasis of GSH and cysteine[3].

GGT and Hypertension: Hypertension is the most common modifiable risk factor for cardiovascular disease, especially in middle-age individuals and the elderly. Recently, GGT has been found to be involved in the pathogenesis of hypertension.[4]. GGT showed strong positive correlations with systolic blood pressure and diastolic blood pressure, while demonstrating a positive linear correlation with body mass index, waist circumference, fasting plasma glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid and high-sensitivity C-reactive protein (hs-CRP) levels. Elevated serum GGT levels within the normal range are considered to be associated with a higher risk of incident hypertension [5].

Elevated levels of GGT are involved in the pathogenesis of CAD: GSH is a tripeptide comprised of three amino acids: gamma-glutamic acid, L-cysteine and L-glycine. Its primary biological function is to act as a nonenzymatic reducing agent to help keep cysteine thiol side chains in a reduced state on the surface of proteins. GSH also prevents oxidative stress in most cells. The physiological role of GGT is to initiate the hydrolysis of extracellular GSH by cleaving the gamma-glutamyl amide bond of the tripeptide to cysteine and other thiol compounds, which are known to promote LDL oxidation by reducing Fe(III) to redox-active Fe(II). [6]. One of the suggested mechanisms for this association is increased transport of glutathione into cells by increased GGT activity, to maintain high intracellular antioxidant glutathione levels in order to compensate for the oxidative stress . Increased serum GGT levels are implicated in increased blood pressure and the progression of hypertension [7]. Some researchers believe that serum GGT is partially adsorbed onto LDL lipoproteins, which can carry GGT activity inside the plaque (in proportion with serum GGT levels), in which free iron has also been described [8]. GGT-mediated reactions catalyze the oxidation of LDL lipoproteins, likely contributing to oxidative events influencing plaque evolution and rupture [9]. The relationship between elevated serum GGT activity and slow coronary flow and found that the mean thrombosis in myocardial infarction frame count showed a positive and moderate correlation with serum GGT activity. Serum GGT activity was the only independent predictor of the mean thrombosis in myocardial infarction frame count [10].

GGT And Heart Failure: It has been shown that elevated serum GGT activity exists in the early stages of heart failure (HF), the final and common pathway of all cardiovascular diseases [11]. The burden of prevalent (HF) will increase due to an aging society, with improved survival of patients incurring acute and chronic coronary disease or with severe hypertension, plus the growing prevalence of obesity and diabetes[12,13]. The primary pathophysiologic mechanism described that is involved in liver dysfunction is transmission of elevated central venous pressure (CVP) to the hepatic venous system leading to passive hepatic congestion. Another mechanism involved in liver injury is the decrease in cardiac output leading to impaired liver perfusion associated with acute hepatocellular necrosis [14]. Other studies have focused on the mechanism of elevated serum GGT levels in HF patients to explore new methods of intervention in HF progression. The role of GGT in reversing pathogenic K^+ channel remodelling in the diseased heart. They found that GSH_o elicits GGT- and reactive oxygen species-dependent transactivation of tyrosine kinase signalling that upregulates K^+ channel activity or expression via redox-mediated mechanisms. The signalling events stimulated by GGT catalysis of GSH may be a therapeutic target to reverse pathogenic electrical remodelling of the failing heart[15] . Higher central venous pressure has also been found to be related to serum GGT levels in HF patients, and abnormal liver function was attributed to increased serum GGT levels . However, further studies should be undertaken to elucidate the mechanism of elevated serum GGT levels in the progression of HF[16].

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MATERIALS AND METHODS

We studied on 80 patients with heart failure who attended for treatment in Baghdad Medical City, the patients characterized in Electromyo Cardio Gram (ECG) for treatment in hospital. The patient samples were divided into 40 Females and 40 Males with ages from 30 to 87 years and 80 normal healthy controls, 40 Males, 40 Females with ages from 27 to79 years. GGT activity by (Szasz methods) [17]. The reagents used R1, buffer Glyclyglycine (62 mmol/L) and tris pH 8.3 preservative (95 mmol/L), R2 substrate from L-G-glutamyl-p-nitroanilide, the absorbance at 405nm was measured. GGT was calculated by using the following equation:

$$IU/L = (\Delta Abs/min) x\ 2121.$$

Glutathione (GSH) concentration was measured in serum according to method of reagent Walden Ellman modified by Al-zamely [18]. The Ellman's reagent (5-5-dithiobis (2-nitrobenzoic acid) was add in phosphate buffer of pH 8.0 (prepared by mixing of 0.6 mol KH_2PO_4 and 0.08 mol K_2HPO_4) then the absorbance at 412 nm was measured.The concentration Glutathione in blood serum was calculated by using the following equation:

$$\text{Conc of GGT } (\mu mol\ mL^{-1}) = (A) \text{ at } 412 \text{ nm} / E_O \times L.$$

$$L = \text{Light Path(cm)}. \qquad E_o = 13600\ M^{-1}\ cm.$$

Sodium, Potassium concentrations, were measured by Kits from Spinreact. co , Spectrum .co, and for chloride from Biolabo. co, with an automatic analyzer.

The current work represents a cross-sectional study, which was conducted during the period from October 2014 to February 2015. Blood samples were collected from 80 normal healthy controls (40 males and40 females) with age ranges from 27-79 years, and 80 patients with hypertension, heart failure, who attended for treatment in Baghdad Medical City, the patients characterized in Electromyo Cardio Gram (ECG) cane to hospital , with age ranges from 30 to 87 years. The blood was allowed to coagulate at room temperature and was centrifuged at 3000 r.p.m. for 15min. and the resulting sera were placed into test tubes and were used for estimation of GGT, GSH and sodium, potassium and chloride concentrations

Statistical analysis: Data expressed as meanes ± SD. Students' t-test used to evaluate differences between the groups .For all tests $P \leq 0.05$ and 0.01 considered statistically significant. All calculations were made using Excel 2007 program for Windows.

RESULTS AND DISCUSSION

Results: A significant increase in the GGT activity in serum of patients with heart failure in males and females compared to control group. There was increase in the GGT activity in serum of patients with heart failure in males and females with increase in age compared to control group. Significant increase in potassium concentration in male patients only compared to control group and significant increase in chloride concentration in male and female patients compared to control group was observed. Results also showed that there is a significant increase in the blood pressure in both male and female patients compared to control group. A significant decrease in serum reduced Glutathione (GSH) levels in male and female patients compared to control group was observed. Gamma-glutamyltransferase (GGT) has been found to be involved in the pathogenesis of cardiovascular diseases, especially coronary artery disease, and the prognosis of cardiovascular disease may be predicted by increasing GGT levels. GGT levels are related to cardiovascular emergencies of chronic heart failure[1]. The results of GGT activity in serum control and heart failure patients are presented in table 1.

Table 1. GGT activity in serum control and heart failure patients.

State	No.	(Mean ± SE) I U/ L	P value
Control	80	13.07 ± 0.66	
patients	80	64.9 ± 1.4	≤ 0.01

Increase in the GGT activity in serum of male patients more than female patients compared to control group .Women who experience heart failure (HF) exhibit distinct differences from men (Table 2and 3). Because women are a minority in major HF trials and because diagnostic criteria have been variable in epidemiologic surveys, differences in sex hormone effects and responses to injury, pressure overload and aging, which may account for differences observed in epidemiology [19].

Table 2. GGT activity in control and HF patients in males according to age

Age (year)	Activity GGT(I U/ L) (Mean±SE)		P value
	Control	Patients	
	Male	Male	
Less than 45	6.77 ± 0.66	42.54 ± 1.5	≤ 0.01
More than 45	13.59 ± 0.15	65.76 ± 1.8	≤ 0.01

Table 3. GGT activity in control and HF patients in females according to age

Age(year)	Activity GGT (I U/ L) (Mean±SE)		P Value
	Control	Patients	
	Female	Female	
Less than 45	8.19± 0.83	38.81 ± 0.77	≤ 0.01
More than 45	15.25 ± 0.46	59.84 ± 3.0	≤ 0.01

The burden of prevalent (HF) will increase due to an aging[12,13]. The role of GGT in reversing pathogenic K^+ channel remodelling in the diseased heart. They found that GSH_o elicits GGT- and reactive oxygen species-dependent transactivation of tyrosine kinase signalling that upregulates K^+ channel activity or expression via redox-mediated mechanisms[15].

Table 4. Activity of electrolytes in control in male and female patients with HF

Activity Electrolytes (mmol\L)(mean ± S E)						
Electrolytes	**Normal**	**No**	**Patients Femals**	**No**	**Patients Male**	**P Value**
Na	135-155	40	136.21±1.5	40	136.12±0.66	≤ 0.05
K	3.5-5.3		3.75±0.083		6.041± 0.13	≤ 0.01
Cl	95-105		320±74		198± 71	≤ 0.05

Results showed no significant in concentration of Na^+ in male and female patients compared to control group but significant increase in K^+ concentration in male patients and in Cl^- concentration in male and female patients compared to control group (Table 4). Studies demonstrating K^+, Cl^- cotransport in rabbit proximal tubules have shown a coupled K^+, Cl^- movement from the cell to peritubular fluid, in addition , several modes of coupled K^+ and Cl^- movement have been shown in K^+ excretion by renal tubules, directly coupled K^+,Cl^- cotransport, parallel K^+ and Cl^- conductance, parallel K^+/H^+ and Cl^- / $HCO3^-$ exchangers and Na^+, K^+, Cl^- , co transport in modeling Cl^- transport in the rat proximal tubule[20]. Studies demonstrating increase K^+ mean there was dysfunction in kidney, and found increase the fluid in the patients cause higher central venous pressure but in Cl^- the increase in concentration because metabolic acidosis which increase the concentration in the blood.

Table 5. SBP and DBP for HF patients and control group of males.

Males	Patients	Control	P value
	Mean±SD	Mean±SD	
SBP (mmHg)	155.00±7.66	124.00±2.58	0.0001*
DBP (mmHg)	91.25±3.89	85.00±2.22	0.0001*

*Significant using t-test for two independent means at 0.05 level of significance

Table 6. SBP and DBP for HF patients and control group of females.

Females	Patients	Control	P value
	Mean±SD	Mean±SD	
SBP (mmHg)	152.00±8.55	124.00±4.11	0.0001*
DBP (mmHg)	90.35±2.29	84.00±4.68	0.0001*

*Significant using t-test for two independent means at 0.05 level of significance.

Results showed there is a significant increase in the blood pressure in both male and female patients compared to control group as in tables 5,6. Hypertension is the most common modifiable risk factor for cardiovascular disease, especially in middle-age individuals and the elderly. Recently, GGT has been found to be involved in the pathogenesis of hypertension.[4].

Table 7. Serum reduced Glutathione in HF patients and control group.

Glutathione(mmol/l)	Control	Patients	P value
	Mean±SD	Mean±SD	
Male	16.24±0.05	13.32±0.04	0.0001*
Female	15.17±0.04	12.25±0.03	0.0001*

*Significant using t-test for two independent means at 0.05 level of significance

Results showed significant decrease in serum reduced Glutathione (GSH) levels in male and female patients compared to control group as in table 7. One of the suggested mechanisms for this association is increased transport of glutathione into cells by increased GGT activity, to maintain high intracellular antioxidant glutathione levels in order to compensate for the oxidative stress. Increased serum GGT levels are implicated in increased blood pressure and the progression of hypertension [7].

APPLICATIONS

The present study is useful to know some of the reasons for Heart failure patients. GGT levels are related to cardiovascular emergencies of chronic heart failure.

CONCLUSIONS

GGT levels are related to cardiovascular emergencies of chronic heart failure. Gamma-glutamyltransferase (GGT), an important enzyme in glutathione (GSH) metabolism.

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