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Gamma Glutamyltransferase Levels and Its Association with High Sensitive C - reactive protein in Sudanese Patients with Type 2 Diabetes Mellitus

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The aim of the study is to examine the relationship between Gamma-glutamyltransferase and the marker of inflammation, i.e., high sensitive C reactive protein, in type 2 diabetic patients in Sudan.
Materials and Methods: A prospective, analytical, hospital based, case control study was carried out Fedail Hospital and Khartoum Teaching Hospital. 100 patients (50 males and 50 females) presenting with type 2 Diabetes Mellitus were enrolled in this study compared to and 50 healthy control subjects from May 2012 to May 2013 were included in the study. Fasting blood glucose, Serum gamma-glutamyltransferase and High sensitive C-reactive protein were measured.
Results: A significant positive correlation between Gamma Glutamyltransferase and high sensitivity-C-reactive protein in patients with type 2 diabetes ($r = 0.431$, $p < 0.001$).
Conclusion: These results suggested that high sensitivity-C-reactive protein levels increase continuously across the fasting blood glucose spectrum starting from the lowest fasting blood glucose in both men and women.

Keyword: Type 2 diabetes Mellitus, Gamma-glutamyltransferase, High sensitive C-reactive protein, Glycated haemoglobin.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, insulin action, or both[1]. Type 2 DM is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. This form of DM, accounts for approximately 90 - 95% of those with DM and was previously referred to as non-insulin dependent diabetes mellitus (NIDDM), or adult-onset DM[1].Type 2 diabetes has been defined according to fasting (FBG) and/or 2-hour blood glucose criteria after ingesting 75 gm oral glucose load (OGTT)[2]. Recently haemoglobin A1C (HbA1c) test has been adopted as a diagnostic criterion for diabetes

[3]. The diagnostic criteria for diabetes are FPG ≥7.0 mmol/L [126 mg/dl]or A1C ≥6.5% (in adults) or 2hPPG in a 75 gm OGTT ≥11.1 mmol/L [200 mg/dl] or Random PG ≥11.1 mmol/L[200 mg/dl][4]. Recent prospective studies have suggested that an elevated level of High sensitive C-reactive protein and Gamma-glutamyltranferase enzyme is associated with subsequent development of diabetes**.** C-reactive protein (CRP) is a nonspecific biomarker of acute inflammation and is produced primarily in the liver. Several prospective studies had shown that serum CRP accelerate or increase the development of diabetes[5, 6] particularly in women[7, 6]. In acute infections, its serum level would be 50- 100 mg/L, but usually not more than 10 mg/L in case of chronic inflammatory conditions like atherosclerosis[8]. The specific diagnostic and predictive role of CRP in many conditions such as cardiovascular diseases, atherosclerosis, diabetes mellitus, trauma, malignancies, etc. is truly disclosed[8]. There is increasing evidence showing that liver enzymes, such as gamma glutamyltransferase (γ-GT or GGT), used as a marker of alcohol consumption or liver disease, show a dose-response relation with incident diabetes even within its normal range[9] and may also predict the development of diabetes in both genders independent of traditionally risk factors[10, 11]. In prospective studies, baseline serum GGT activity predicted future diabetes, hypertension, stroke, and myocardial infarction[12, 13]. Among these diseases, serum GGT within the reference interval most strongly predicted incident type 2 diabetes[14, 15, 16].

2. Material and methods

The study was conducted from May 2012 to May 2013 at Fedail Hospital and Khartoum Teaching Hospital. A total of one hundred and fifty subjects were enrolled for this study. Out of these, fifty were healthy controls [twenty-five males and twenty-five females with mean age 57.3±9.3 years] and a hundred were type 2 diabetics [fifty males and fifty females with mean age 54.8±8.2 years].

The local ethics committee approved the study. Before participation, volunteers were fully informed of the nature and purpose of the study and written consent was obtained from each.

2.1. Inclusion criteria

Type 2 DM was diagnosed on the basis of American Diabetes Association 2008 criteria [fasting plasma glucose ≥126.0 mg/dl after repeat testing or Postprandial ≥200 mg/dl or HbA1c ≥6.0%][1]. And all subjects were non-alcoholics and non-smokers.

2.2. Exclusion criteria

Subjects with nutritional deficiency or active inflammatory diseases were excluded from the study.

2.3. Biochemical measurements

Venous serum and plasma were collected into lithium heparin tubes. Fasting blood glucose concentrations was measured by enzymatic glucose oxidase-peroxidase [GOD-POD] & GGT hepatic enzyme levels were measured by Enzymatic colorimetric assay using Cobas Integra 400 plus with normal serum level of GGT in this method was considered <40 U/L, HbA1c was measured using an immuno-turbidimetry method on [Cobas Integra 400 plus Roche Diagnostics]. The HbA1c concentration was calculated by using the formula: [calculated HbA1c (%) = A1c/Hb-WB*100].

High sensitive C-reactive protein [hs-CRP] levels were measured by using Immuno-turbidimetric assay on Hitachi 902 with a reference range <5.0 mg/l.

2.4. Statistical evaluation

Data were expressed as mean±standard deviation (SD). The means were compared using Independent sample t.test. Pearson's correlation analysis was used for correlation of parameters measured. Analysis was two-tailed and a p-value ≤0.05 was considered as statistically significant.

3. Results

Baseline characteristics of the type 2 diabetic patients and controls are given in Table 1.

Baseline clinical characteristics, age did not differ in type 2 diabetic patients and controls (p = 0.10). Mean fasting plasma glucose, HbA1C levels of type 2 diabetic subjects were significantly higher than control subjects (p < 0.001) (Table 1).

Table 1: Baseline characteristics of type 2 diabetic subjects and healthy control

Study Group		Mean±SD	P Value
Age [Years]	Type 2 DM[n=100]	54.8±8.2	0.1
	Control[n=50]	57.3±9.3	
FBG [mg/dl]	Type 2 DM[n=100]	228.8±66.1	0.00*
	Control[n=50]	98.4±7.8	
HbA1C [%]	Type 2 D [n=100]	9.3±2.1	0.00*
	Control[n=50]	5.3±0.6	
hs-CRP [mg/l]	Type 2 DM[n=100]	26.4 ±21.3	0.00*
	Control[n=50]	3.4±0.8	
GGT [u/l]	Type 2 DM[n=100]	35.1±21.2	0.00*
	Control [n=50]	16.6±5.7	

*P value considered sig ≤ 0.05

Mean hs-CRP levels in type 2 diabetic subjects (26.4±21.2 mg/l) were higher than the values in controls (3.36±0.86 mg/l) and were found to be statistically significant (p<0.001) (Table 1). A similar trend was observed in GGT values in type 2 diabetic patients when compared with controls (p <0.001).

Further, a significant positive correlation were observed between Fasting blood glucose, hs-CRP (r = 0.635, p = 0.00) and between GGT and hs-CRP in subjects with type 2 DM (r =0.431, p =0.00) (Table 2), (Figure 1, 2 &3).

Table 2: Pearson's correlation analysis between values of FBG, hs-CRP & GGT in patients with type 2 DM.

Correlated variable	FBG & hs-CRP	FBG & GGT	hs-CRP & GGT
R	0.635	0.457	0.431
P	0.00	0.00	0.00

4. Discussion

It has been clearly demonstrated that serum GGT levels even within normal range is predictors of future heart disease, hypertension, stroke, and type 2 DM[19, 17, 20].

C-reactive protein synthesized by the liver as a marker of systemic inflammation has been shown to be associated with Metabolic Syndrome, DM, and cardiovascular disease[21]. Indeed, oxidative processes are components of chronic inflammation acting on different pathways and stimulating the inflammatory response. It has been shown that an association exists between serum GGT and CRP level[22].

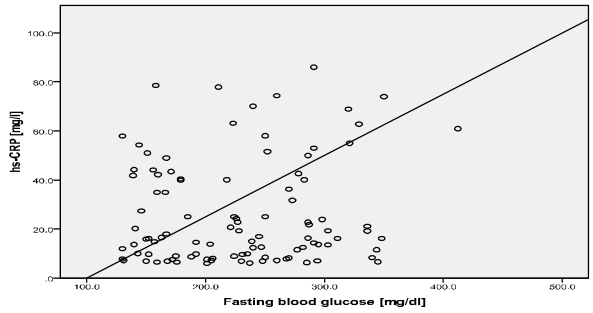

Figure 1: The correlation between FBG and hs-CRP among type 2 DM

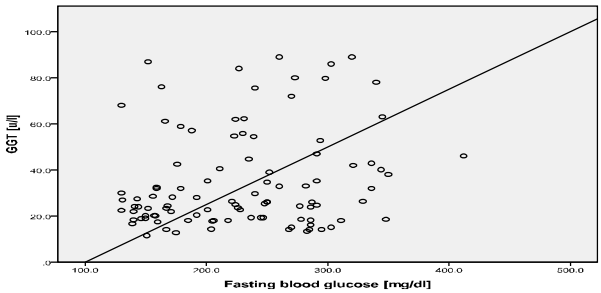

Figure 2: The correlation between FBG and GGT among type 2 DM

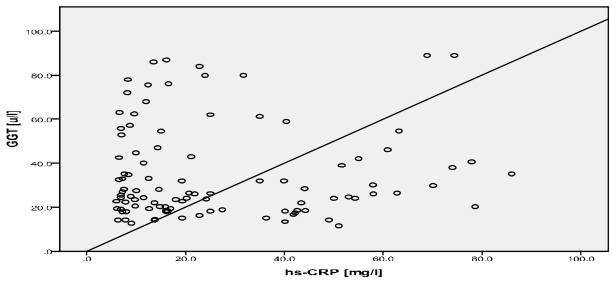

Figure3: The correlation between hs-CRP and GGT among type 2 DM

Nakanishi *et al.*[23] reported that GGT activity was related to the development of impaired fasting glucose or type 2 DM. These authors also found an association between serum GGT and white blood cell count and stated that this finding could provide evidence for subclinical inflammation as an underlying mechanism[23].

This study determined the relation between Fasting blood glucose levels; GGT and hsCRP in type 2 DM, showed that GGT and hsCRP levels increase continuously across the spectrum of FBG, starting from the lowest FBG in both men and women.

In the present study, a significantly high ($p < 0.001$) increase in serum GGT was observed in type 2 diabetics compared to healthy controls. The results were in accordance with many prospective studies where strong relationship between GGT concentration and incident of diabetes have been observed in non-alcoholics independently of classical cardiovascular risk factors[17, 18, 19].

The results of the study also indicate a significant increase in values of hs-CRP ($p<0.001$) in diabetic subjects when compared to healthy controls.

5. Conclusion

The present study showed that hsCRP and GGT levels are strongly associated with type 2 Diabetes Mellitus. However, this study may prove important in future to assess the GGT and hs-CRP levels in type 2 diabetic subjects with complications and to evaluate the severity of complications.

6. Competing interests

The authors declare that there are no conflicts of interests.

7. Acknowledgments

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