Gamma Glutamyl Transferase and C- Reactive Protein in Type 2 Saudi Diabetic Patients in Relation to Management Modality and Components of Metabolic Syndrome

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Abstract:

Background: Different management modalities are used to control hyperglycemia associated with type 2 diabetes (T2DM). Research has indicated an association of single or combined insulin therapy with increased cardiovascular events. Metabolic syndrome (MS), as well as increased levels of C- reactive protein (CRP), and gamma glutamyl transferase (GGT) are also associated with increased CVD risk.
Aim: To study the relationship between management modality, glycaemic control, components of metabolic syndrome and serum levels of GGT and CRP
Methods: T2DM subjects were recruited from outpatients clinics at two hospitals in Jeddah. Pregnant subjects, and those having any other severe chronic illness or diabetes complications were excluded. Anthropometric measurements, and blood pressure were taken. Treatment plan was recorded. Fasting blood samples were obtained to measure Glucose, glycated hemoglobin (HbA1c), lipids profile, CRP and GGT.
Results: A total of 153 subjects were recruited (46.4% males, 53.6% females). MS was present in 142 (92.8%) patients. In spite of significantly lower mean HbA1c in hypoglycaemic drugs users compared to means in those using single or combined insulin therapy (p<0.001), and significantly lower mean diastolic blood pressure (DBP) in insulin users (p = 0.025), no significant difference was found in means of GGT or CRP. Significantly higher mean GGT was found in uncontrolled compared to controlled, and hypertensive compared to normotensive patients (p< 0.05 in both cases). GGT correlated positively with triglycerides (r=0.248, p=0.021), and negatively with high density lipoprotein- cholesterol (HDL- C) (r =-0.254 ,p=0.036). CRP correlated positively with waist circumference (r = 0.27,p=0.020), and mean value being higher in abdominally obese group compared to non-obese (p= 0.018)
Conclusions: Serum GGT and CRP levels do not appear to be affected by management regimen in T2DM Saudi patients. Some components of MS, hypertension and poor glycaemic control are associated with higher levels of either CRP or GGT, hence increased cardiovascular risk.

Introduction:

Type 2 diabetes mellitus (T2DM) is highly prevalent amongst the adult population of Saudi Arabia. Due to the increasing number of available choices to control the associated hyperglycemia, lack of Saudi guidelines, treating physicians have become increasingly uncertain of best management policy (1). Strict glycemic control over time has long been reported to decrease microvascular complications associated with the disease (2-4). In spite of the fact that insulin therapy is very effective in controlling all levels of hyperglycemia, as well as coexisting dyslipidemia (5), it was reported to increase frequency of severe hypoglycemic episode (6). In addition, use of insulin therapy was associated with increased risk of cardiovascular disease (CVD) directly (7), or indirectly due to weight gained following insulin therapy (8). Increased risk of CVD has also been associated with the presence of metabolic syndrome (9,10), as well as increased levels of C- reactive protein (CRP) (11,12), and gamma glutamyl transferase (GGT) (13,14). The aim of our study is to understand the relationship between management modality, glycaemic control, components of metabolic syndrome and serum levels of GGT and CRP

Methods:

Patients diagnosed with type 2 diabetes mellitus, were randomly recruited from the diabetes out-patients clinics at King abdulaziz university hospital and King Fahad Armed forces hospital (KFAFH) in Jeddah, Saudi Arabia, during the course of one month (1st of June to 2nd of July, 2014). Ethical approval was obtained from the Committee on the Ethics of Human Research at the ‘‘Faculty of Medicine- King Abdulaziz University’’, and the Committee on the Ethics of Medical Research at KFAFH Willing patients were asked to sign an informed consent form to participate. Exclusion criteria included: pregnancy, having any other severe chronic illness or diabetes complications (i.e. end stage renal disease, liver disease, recent myocardial infarction, etc). Blood pressure was measured following the recommendations of the American Heart Association Council (15), using a standard mercury sphygmomanometer with the cuff on the right upper arm. Two blood pressure readings; one minute apart; while the subject was seated for 10 minutes were taken, and the mean of the two readings was calculated. Anthropometric measurements were taken for all. Height was measured bare footed to the nearest 0.5 cm using a stationary stadiometer. Weight was measured to the nearest 0.5Kg while wearing light street clothing using a calibrated scale. Both measurements were used to calculate body mass index (BMI). Waist measurements was taken at the level of the umbilicus, and hip measurement at the maximal protrusion of the gluteal muscles, both to the nearest 0.5 cm. BMI was used to classify patients as being normal (18.5- < 25), overweight (25- <30), or obese (≥ 30) (16). In addition, a questionnaire comprising the demographic and management plan that the patient was following to control his/her diabetes was filled during face-to-face interview. Treatment plan was recorded as, lifestyle modification (i.e. diet and exercise), oral hypoglycemic agents (metofrmin, sulfonylurea, alpha glucosidase inhibitor, thiazolidinedione, or DPP4 inhibitor), insulin, non-insulin injectable drugs (GLP-1 agonist), or any combination of them. Fasting blood sample was obtained for measurement of glucose, glycated haemoglobin (HbA1c) lipids profile, high sensitivity CRP (hs- CRP) and GGT. Serum glucose and lipids (cholesterol, triglycerides and high density lipoprotein (HDL-C) were assayed using automated enzymatic methods (Dimension Vista 1500T Intelligent Lab System from SIEMENS Company) at the biochemistry laboratory. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation (17). Glycated haemoglobin (HbA1c) analysis was performed on Dimension Vista 1500T Intelligent Lab System (SIEMENS Company). Hb A1c ≤ 7 % was considered controlled and Hb A1c of >7% Was considered uncontrolled, in accordance to the American Diabetic Association Guidelines (18). Hypertension was defined as a systolic blood pressure >140 mm Hg, and/ or diastolic blood pressure >90 mm Hg or current use of antihypertensive medications (19). The consensus definition (20) was used to diagnose metabolic syndrome.

Statistical Analysis: Data was entered, coded, and analyzed using SPSS version, 20. Descriptive statistics, such as mean ± SD, were calculated for all estimated parameters. Comparison between two means was performed using unpaired Student t-test for normally distributed, and the Mann Whitney-U test for non-normally distributed parameters. Differences between more than two means were tested using One way ANOVA analysis. Chi square test was used for categorical variables. All p values that were <0.05 were deemed statistically significant.

Results:

A total of 153 subjects were recruited (46.4% males, 53.6% females). Characteristics of study group according to gender is presented in Table 1

Table 1: Anthropometric, demographic and clinical characteristics of study group

Variable	Male (N = 71)	Female (N= 82)	*P*-value
Age (Mean ± SD) years	55.97 ± 11.53	60.38 ± 10.11	***P* = 0.021**
BMI (Mean ± SD)	30.55 ± 5.41	32.55 ± 6.06	***P* = 0.033**
Percentages according to BMI Classes: Healthy weight / overweight / obese	14.3% / 34.3% / 51.4%	12.3% / 18.5% / 69.1%	*P* = 0.059
Duration of Diabetes (years)	12.42 ± 8.40	11.57 ± 8.00	*P* = 0.529
Systolic BP (mm Hg) (Mean ± SD)	125 ± 19	129 ± 18	*P* =0.248
Diastolic BP (mm Hg) (Mean ± SD)	74± 11	78 ± 11	***P* = 0.016**
Percentage of Hypertensive subjects	80.0 %	81.5%	*P* = 0.818
Percentage of subjects with Metabolic Syndrome	90.1%	96.3%	*P* = 0.122
Waist Circumference (Cm) (Mean ± SD)	110.2 ± 13.8	107.7 ± 12.1	*P* = 0.232
Percentage of subjects with Abdominal Obesity (>102 cm for males, and > 88 cm for females)	69.1%	92.7%	***P* < 0.001**

Female subjects had a significantly higher mean age, and BMI, and DBP. Females also had a significantly higher percentage of abdominal obesity.
Results of measured biochemical parameters and blood pressure; expressed as mean ± SD; after dividing subjects according to treatment modality are presented in Table 2

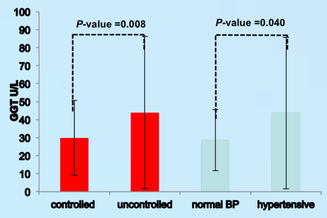
Table 2: Measured biochemical variables and blood pressure according to treatment modality (Mean ± SEM).

Variable	Mean ± SEM In users of Oral hypoglycemics (N = 83)	Mean ± SEM In Insulin users (N = 20)	Mean ± SEM In users of Combination therapy (N = 50)	*P*-Value
HbA1c (%)	7.68 ±0.16	9.99 ±0.62	9.45 ±0.28	***P*<0.001**
Glucose (mg/dl)	153 ±13.2	148 ±12.4	153 ±17.2	*P*= 0.416
hs-CRP (mg/L)	4.52 ±0.63	5.46 ±0.72	4.41 ±0.56	*P*= 0.572
GGT (U/L)	44 ±6.9	35 ±10	43 ±6.1	*P*= 0.774
DBP (mm Hg)	76 ±1.4	70 ±2.7	78 ±1.5	***P*= 0.025**
SBP (mm Hg)	127 ±2.3	122 ±3.9	128 ±2.2	*P*= 0.430

In spite of significantly lower mean HbA1c in hypoglycaemic drugs users compared to means in those using single or combined insulin therapy (p<0.001), and significantly lower mean diastolic blood pressure (DBP) in insulin users (p = 0.025), no significant difference was found in means of GGT or hsCRP.

Comparing mean GGT in subjects with good glycaemic control to mean in uncontrolled subjects, the latter was found to be significantly higher (P = 0.008). Significantly higher mean GGT was also found in hypertensive compared to normotensive patients (P=0.04) (Figure 1).

Figure 1: GGT level (Mean ± SD) in subjects with adequate glycaemic control vs. uncontrolled subjects, and in hypertensive vs normotensive subjects.

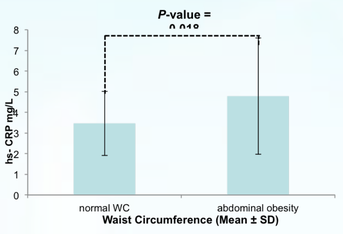


Studying the relationship between levels of GGT and hsCRP in all subjects and different components of the metabolic syndrome, GGT was found to correlate positively with triglycerides, and negatively with HDL- C, but hsCRP correlated positively with waist circumference only (Table 3). Furthermore, the mean value of hsCRP was significantly higher in abdominally obese group compared to non-obese (Figure 2)

Table 3: Correlations of hs-CRP, and GGT with different components of metabolic syndrome in all studied subjects.

	GGT	CRP	HbA1c	HDL- C	TG	WC	DBP
GGT		*R*=0.141 (*p*=0.229)	*R*=0.063 (*p*=0.519)	*R*= -0.254 (*p*=0.036)	*R*= 0.248 (*p*=0.021)	*R*= -0.099 (*p*=0.307)	*R*= 0.001 (*p*=0.989)
CRP	*R*=0.141 (*p*=0.229)		*R*= 0.009 (*p*=0.941)	*R*= -0.023 (*p*=0.870)	*R*= -0.029 (*p*=0.826)	*R*= 0.270 (*p*=0.020)	*R*= -0.048 (*p*=0.689)
HbA1c	*R*=0.063 (*p*=0.519)	*R*= 0.009 (*p*=0.941)		*R*= -0.101 (*p*=0.348)	*R*= 0.210 (*p*=0.028)	*R*= 0.055 (*p*=0.533)	*R*= 0.004 (*p*=0.968)
HDL- C	*R*= -0.254 (*p*=0.036)	*R*= -0.023 (*p*=0.870)	*R*= -0.101 (*p*=0.348)		*R*= -0.292 (*p*=0.009)	*R*= -0.134 (*p*=0.215)	*R*= 0.018 (*p*=0.866)
TG	*R*= 0.248 (*p*=0.021)	*R*= -0.029 (*p*=0.826)	*R*= 0.210 (*p*=0.028)	*R*= -0.292 (*p*=0.009)		*R*= 0.074 (*p*=0.453)	*R*= 0.113 (*p*=0.257)
WC	*R*= -0.099 (*p*=0.307)	*R*= 0.270 (*p*=0.020)	*R*= 0.055 (*p*=0.533)	*R*= -0.134 (*p*=0.215)	*R*= 0.074 (*p*=0.453)		*R*= 0.110 (*p*=0.195)
DBP	*R*= 0.001 (*p*=0.989)	*R*= -0.048 (*p*=0.689)	*R*= 0.004 (*p*=0.968)	*R*= 0.018 (*p*=0.866)	*R*= 0.113 (*p*=0.257)	*R*= 0.110 (*p*=0.195)	

Figure 2: hs-CRP concentrations in subjects with normal and abdominal obesity (Mean ± SD) .



Discussion:

Diabetes mellitus (DM) is associated with a myriad of micro-, and macro- vascular complications. Hyperglycemia, increased blood pressure, dyslipidemia (components of metabolic syndrome), inflammation, and oxidative stress are all characteristics of DM, and are implicated in the development of these complications (21-27), so that their control leads to decreased risk of both complications (2, 6, 28-32). Monitoring of glycemic control, blood pressure, and lipids profile are routinely carried out in diabetic patients, with treatment adjusted as need be to achieve better control. However, monitoring of inflammation and oxidative stress is not commonly performed.
In comparatively recent studies, C-reactive protein (CRP) was suggested; based on multiple prospective epidemiological studies; as a marker of inflammation that can help in predicting macrovascular complications, and their clinical outcomes (11, 33- 38). Moreover, studies also indicated that CRP is a stronger predictor of increased cardiovascular risk than the more traditional low-density lipoprotein cholesterol (LDL- C) (39), and its level did not correlate to that of LDL- C (39, 40). Hence, it can be used as an adjunct measurement to lipids profile for better risk stratification. Our results validate earlier reports of lack of correlation with all forms of serum cholesterol, but indicate a significant correlation with abdominal obesity, a major component of the metabolic syndrome. This can be explained by the known relationship between obesity generally; and abdominal obesity in particular; with systemic inflammation (41).
In spite of its proven strength in risk stratification of macrovascular complications, CRP is not carried out in diabetic Saudi patients routinely or even periodically. In view of the biochemical stability of this biomarker, the standardization of the high sensitivity assay, and its strength as a risk predictor it might be prudent to add it to monitor diabetic patients to identify those apparently normal lipid profile individuals in need of additional testing and extra lipid management.
Measurement of oxidative stress in clinical settings has its limitations. An important antioxidant defense in human tissues is the tri-peptide reduced glutathione (GSH), with oxidative stress occurring in case of its inadequacy. Lower levels of GSH in diabetic patients was found to be associated with increased risk of micro-vascular complications (42-44). However, estimation of GSH status is not possible in a clinical setting, and the search was on for a more practical marker. A breakthrough came when studies indicated that serum level of GGT can be used as an *in- vivo* biomarker of GSH status, due to its role in recycling GSH precursors in almost all tissues (45- 47). Furthermore, it was reported that elevated levels of GGT; even within the clinically normal range; are associated with increased risk of incident type 2 diabetes, hypertension and cardiovascular events, making it an independent risk factor for the development of cardiovascular or cerebrovascular diseases (13, 14, 48). However, and in spite of the accumulating evidence of its value as a risk predictor of vascular injury in metabolic disease,
GGT is still being used as a marker of alcohol consumption or liver disease exclusively. Our report shows a correlation between its level and the dyslipidemia associated with the metabolic syndrome, as well as its increased mean in poorly controlled and hypertensive diabetics that supports earlier reports. Indeed, it could be suggested that the addition of GGT estimation to the tests requested routinely for diabetic patients would help in early detection of microvascular complication

Conclusions:

Serum GGT and hs- CRP levels do not appear to be related to management regimen in T2DM Saudi patients. Poor glycemic control and hypertension are associated with higher mean GGT. Not surprisingly, serum hsCRP correlates with waist circumference, however, GGT correlates positively with triglycerides, and negatively with HDL- C, known components of metabolic syndrome. Due to their value as independent risk predictors of vascular injury they should be included in routine monitoring of diabetic patients. Further studies are needed to understand how these markers will ultimately lead to CVD risk prediction and how targeting these markers with conventional and contemporary measurements will lead to CVD risk reduction.

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