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Correlation of Gamma Glutamyl Transferase and Insulin Resistance in First Degree Relatives of Type 2 Diabetics

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ABSTRACT

Background: Serum gamma glutamyl transferase (GGT) concentration within its normal reference range has emerged as an important biomarker in the pathogenesis and diagnosis of different diseases in general population. **Aim and Objective**: The objective of the present study was to investigate correlation of GGT with insulin resistance in healthy people having first degree relatives as a diabetic. Determining insulin resistance in general population is difficult because of difficulties in measuring insulin levels because of its sampling precautions. Therefore, routine chemistry tests like serum GGT, triglycerides and HDL-C are chosen because they are cost-effective and sensitive to indicate the presence of insulin resistance. **Subjects and Methods**: A total of 100 males and females were investigated. Family history of diabetes, blood pressure and other demographic data were collected. Serum fasting lipids, glucose and liver enzymes were performed by automated chemistry analyzer. Insulin resistance was calculated from triglyceride/HDL ratio. Pearson correlation was applied to find a correlation between GGT and insulin resistance. **Results**: A significant difference *p*-value <0.05 was present between serum GGT levels of controls and subjects. The male subjects were younger and showed higher values than controls for serum GGT, triglycerides and HDL which were significantly different (*p*-value <0.05). GGT was correlated to insulin resistance showing weak positive correlation with insulin resistance. **Conclusion**: In normo-glycemic first degree relatives of diabetics, serum GGT levels were significantly higher and showed a weak positive correlation with insulin resistance in males.

Key Words: GGT, Insulin resistance, Type-2 diabetes, Correlation.

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by high blood glucose levels due to defects in insulin secretion, function or both. The chronic hyperglycemia of DM is associated with long term damage, causing microvascular and macro vascular complications. The classification of DM adopted by World Health Organization (WHO) falls into two broad categories *i.e.* type1 DM with absolute deficiency of insulin while, type2 DM is described for combination of resistance to insulin actions or an inadequate compensatory insulin secretory response[1]. Type 2DM frequently goes undiagnosed for many years because hyperglycemia develops gradually and at earlier stages is not severe enough for the patients to note any of the classic symptoms of the disease[2,3,4]. There is epidemiological evidence that retinopathy occurs before clinical diagnosis of type 2 DM is made[2].

Insulin resistance (IR) can be illustrated as a subnormal response to both endogenous and exogenous insulin. It occurs at the level of skeletal muscle, liver and adipose tissue and cause impaired insulin secretion from the pancreas.[5] IR is the hall-mark of obesity, metabolic syndrome and many cardiovascular diseases[6]. As the sensitivity of target

tissues decrease, there is increase in blood glucose levels and increased production of atherogenic lipids.[7] The damage to liver in IR is due to increased production of free fatty acids which are toxic to hepatocytes. Abnormalities of triglyceride storage and lipolysis are detectable earlier than fasting hyperglycemia[8]. Shulman suggested that raised in plasma fatty acid concentration initially induces insulin resistance by inhibiting glucose transport or phosphorylation activity followed by reduction in muscle glycogen synthesis and glucose oxidation[9]. This reduction in insulin activated glucose transport and phosphorylation activity is seen in obese individuals[10], patients with type 2 diabetes[11] and lean, normo-glycemic insulin resistant off-springs of type 2 diabetic individuals[12]. Insulin resistance (IR) is the inability of the insulin to produce its common biological effects.[13] IR can develop in all facets of insulin action. As IR occurs prior to the diagnosis of different disease states, identifying it in the general population has certain preventive significance.[14] Clinical practices around the world apply different criteria for stratification of patients according to the changes in the lab tests. One of the objectives is to facilitate early detection of the disease. The presence of IR allows for identifying subjects at risk of develop in different diseases including diabetes and heart disease. Diagnosis of IR is difficult because it manifests itself subclinically. There are different methods of measuring insulin sensitivity; hyperinsulinemic-euglucemic clamp technique is the soundest technique.[15] Other methods include fasting insulin, glucose insulin ratio, homeostatic model assessment, McAuley index etc.[16] All of these tests require fasting insulin levels which are difficult to obtain in general population. The product of fasting glucose and triglyceride is also proposed however it is expressed by a logarithmic scale[17]. Due to association of IR with dyslipidemia, Triglyceride/ HDL-C has been used to evaluate IR. Studies in adult population have suggested that plasma concentrations ratio of triglyceride/HDL-cholesterol provides a simple way to identify IR in apparently healthy individuals[18].

Non-alcoholic fatty liver disease (NAFLD) is a clinic-pathological condition representing a spectrum of histological findings due to fat accumulation in hepatocytes without inflammation. NAFLD is diagnosed in clinical setting using detailed techniques such as liver biopsy and ultrasound imaging. However patients with NAFLD are commonly characterized by elevating circulating markers of liver injury including AST, ALT and GGT[19].

GGT is an enzyme which is located on the outer surface of plasma membrane where it facilitates the synthesis of anti-oxidant glutathione. The role of GGT is to initiate the degradation of extra-cellular glutathione (GSH) by hydrolyzing the gamma-glutamyl-cysteine bond in GSH. There is evidence that serum GGT activity is a potential early and sensitive marker of inflammation and oxidative stress.The hepatocellular damage caused by the fatty liver would stimulate the synthesis of GGT or excess fat could enhance oxidative stress leading to over-consumption of GSH with a compensatory increase in GGT.[20] Perry and associates in a prospective cohort study of general population sampling middle-aged men found a strong, independent and graded association between serum GGT levels within normal range and incidence of type 2DM.[21]

In this study we measured serum GGT levels in first degree relatives and calculated insulin resistance with the formula of Tg/HDL-C ratio and focused on the correlation between the two.

SUBJECTS AND METHODS

Prior to the start of study informed and written consent was taken from all participants. A total of 100 subjects were selected including 50 males and 50 females to carry out this study. In each group of males and females, 25 were healthy controls and 25 were norm-glycemic subjects with a first degree relative as a diabetic. Participants were selected from general population with and without family history of diabetes. The age of participating was ranging from 25-55 years. Various demographic parameters including height, weight, body mass index (BMI) and blood pressure were recorded. The height was measured on a standard height scale and weight was measured on CAMRY weight scale. BMI was calculated by the following formula; BMI=weight (kg)/height (m^2).

After an overnight fast, 6ml of blood was

drawn aseptically and was centrifuged to separate the serum for further analysis. It was divided into 2 aliquots, one for glucose, and one for lipid profile and liver function tests. All the biochemical parameters including lipid profile, glucose and liver function tests were analyzed by Auto- chemistry analyzer Dimension RXL by DADE Behring (USA) using standard protocols. Insulin resistance was calculated from the formula Tg/HDL-C ratio. The data was analyzed by using SPSS17. Mean±SEM is given for quantitative variables. Independent t-test was applied to observe group mean differences. Pearson Correlation was applied. Correlation was calculated with p value of <0.05 was considered as statistically significance.

RESULTS

In this cross-sectional study, total 50 males and 50 females were included. Controls and subjects were age and sex matched. Other demographic parameters including blood pressure and BMI are given in Table I.

Table 1: Comparison of age, BMI and blood pressure of male and female cases and controls.

	Controls	Cases	p-value
Male			
Age (years)	45.88±1.04	41.28±1.73	0.038*
BMI (kg/m2)	24.72±0.52	25.22±0.66	0.67
BP (Systolic)	122±1.53	127±1.66	0.043*
BP (Diastolic)	78.00±1.12	83.00±1.29	0.01**
Female			
Age (years)	43.24±1.43	46.12±1.12	0.79
BMI (kg/m2)	26.48±0.77	28.11±0.80	0.53
BP (Systolic)	126±2.57	126.80±2.14	0.64
BP (Diastolic)	84.88±1.40	83.60±1.74	0.23

p<0.05significantly different from controls.
p<0.01 highly significant as compared to controls.

Table 1 shows significant difference in age and BP of male subjects. They are younger and have higher BP as compared to their counterparts. No significant difference was seen in female controls and subjects.

Table 2 shows the male subjects had significantly higher triglycerides and GGT levels and lower HDL levels whereas no significant difference was seen in female controls and subjects.

Table 2: Comparison of serum glucose, lipid profile and liver function tests of controls and subjects.

Group	Controls	Treated
Male		
Cholesterol (mg/dl)	178.88±5.10	184.24±7.88
Triglycerides (mg/dl)	105.72±5.48	134.48±9.97*
HDL (mg/dl)	40.96±1.16	36.24±1.33*
LDL (mg/dl)	116.68±4.42	114.64±5.77
Glucose	84.40+2.54	91.72+3.89
GGT	24.84+1.77	35.64+3.30**
Female		
Cholesterol (mg/dl)	190.52±5.41	184.00±6.75
Triglycerides (mg/dl)	107.64±10.32	101.76±6.95
HDL (mg/dl)	46.20±1.45	45.04±1.55
LDL (mg/dl)	130.76±6.07	116.32±6.00
Glucose	81.24+3.09	81.24+2.68
GGT	26.56+3.38	26.12+2.08

*p<0.05 significantly different as compared to controls

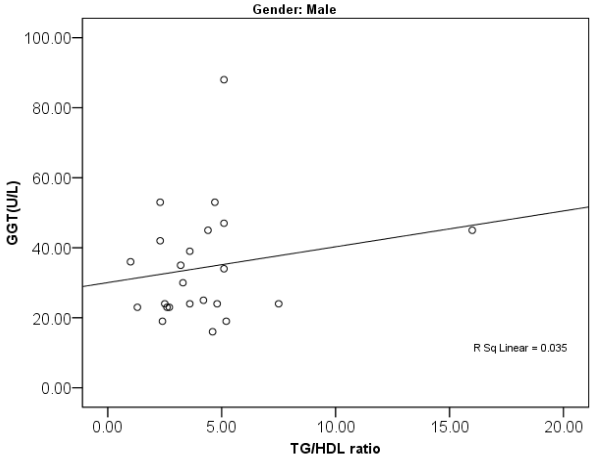

Fig. 1. Regression line between GGT and Tg/HDL ratio

In Figure 1 the regression line shows a weak positive correlation between GGT and Tg/HDL-C ratio only in male subjects.

DISCUSSION

A clustering of risk factors including hyperinsulinemia, elevated triglycerides, decreased high density lipoproteins (HDL) cholesterol and hypertension is often observed in the setting of insulin resisitance.[22] The male subjects in our study

had all these characteristics. Their blood pressure and triglycerides were significantly raised and their HDL-C was significantly decreased.

As liver has been recognized as a major target of injury in patients with IR, even in the non-diabetic patients elevated plasma liver enzymes levels are a risk factor for the development of type 2 diabetes. In this study aspartate aminotransferase (AST) was not significantly raised, however alanine aminotransferase (ALT) and GGT were significantly raised in male subjects. GGT was chosen because it has emerged as an important predictor in the pathogenesis of diabetes even in its normal range. Also serum GGT levels within its normal range have predicted oxidative damage.[23] In a study, Wallace and associates raised the possibility that in men GGT rather than AST or ALT, is a more sensitive marker of insulin sensitivity independently of body fat measure.[24] However Hanley and associates in their study proposed AST and ALT were significantly associated with 5 year risk of incident diabetes.[25] As patients of IR frequently presented with alterations in lipid profile Tg/HDL-C ratio was chosen to represent IR. In a study by Ateia and associates in comparing different indices of IR, they found out that TG/HDL-C ratio was useful and a practical approach to identify IR[26]. Yu Xu and associates propose in their study that GGT was independently associated with an increase in the index of HOMA-IR[27], however our study hinted only at weak positive correlation between GGT and Tg/HDL-C ratio.

Although a strong positive correlation has not emerged however the results of different parameters show that all of them are important even in healthy subjects and even in their normal ranges. Perhaps broader studies might indicate how we can use them effectively in routine checkups of the people at risk.

Conflict of interest

Authors have no conflict of interest.

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