

Determination of the Gamma Glutamyl Transferase (GGT) Activity in Gestational Diabetes

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Abstract:

Background and Objective: Liver plays an important role in regulating glucose levels in the body. The liver enzyme gamma-glutamyl transferase (GGT), is a common marker of liver function and has also been associated with insulin resistance, which can be a precursor to gestational diabetes and type 2 diabetes. The aim of this study was to evaluate serum GGT in gestational diabetics.

Materials and Methods: The cross sectional study was conducted between department of biochemistry and gynecology during June to November, 2016 in Erbil city. Blood specimens were collected in the diabetic center in Maternally Teaching Hospital after diagnostic by gynecologist. A total 50 cases were considered as Group I (GDM) and 50 were Group II controls (normal healthy pregnant women). Patient group also subdivided into three subgroups; subgroup 1 GDM first time, subgroup 2 GDM second time and subgroup 3 regard as diabetic patient type 2.

Results: There were statistically significant differences at the level (p value <0.001) elevations in serum GGT in GDM compared with control group, also uric acid, and calcium were increased in GDM.

Conclusions: Our finding showed that increase serum GGT level is an independent risk factor for GDM and identified as high risk factor for GDM.

Keywords: Gamma- glutamyl transferase (GGT), Gestational diabetes mellitus (GDM), Pregnancy.

Introduction:

Diabetes mellitus is the commonest endocrine disorder encountered in clinical practice, defined as a syndrome characterized by hyperglycemia with disturbance of carbohydrate; proteins; and fat metabolism due to an insulin resistance and an absolute or relative lack of insulin. Diabetes is classified into three categories, type 1, type 2 and gestational⁽¹⁾.

Gestational diabetes mellitus (GDM) is any degree of glucose intolerance with first onset or recognition in pregnancy. Cause of GDM includes metabolic and hormonal changes. Patients with GDM frequently return to normal in

postpartum. GDM has increased dramatically in recent decades and is now the most common complication of pregnancy. It can lead to adverse outcomes including larger-than-normal babies and subsequent delivery complications. Women with gestational diabetes are seven times more likely to develop type 2 diabetes later in life, and their children are at greater risk of becoming obese and developing diabetes themselves⁽²⁾.

Risk factors for GDM include; body mass index > 30 Kg/m²; gestational diabetes in previous pregnancy; age of pregnant woman lower than 25 years;

family history of diabetes; ethnicity belonging to a non-white ethnic group; previous delivery of a large baby; and previous stillbirth⁽³⁾.

Gamma-glutamyl transferase (GGT) (EC 2.3.2.2) is found in high level in the liver, kidney, pancreas, heart, and brain. GGT is a transferase (a type of enzyme) that catalyzes the transfer of gamma-glutamyl functional groups, from molecules such as glutathione to an acceptor that may be an amino acid, a peptide or water forming glutamate⁽⁴⁾.

The most abundant natural substrate is glutathione. Glutathione is extracellular and cannot transport through the cell membrane. Glutathione can be broken down into three amino acids (glycine, cysteine and glutamate). GGT activity, normally found in the plasma membrane of virtually all cells except erythrocytes, catalyzes the first step in the degradation of extracellular glutathione (GSH), allowing the precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis⁽⁵⁾.

The general reaction is:

(5-L-glutamyl)-peptide + amino acid \leftrightarrow peptide + 5-L-glutamyl amino acid.

Thus GGT activity favors the cellular supply of GSH, the most important non protein antioxidant of the cell. However, there is also clear evidence that the degradation of GSH can play a pro-oxidant role⁽⁶⁾. GGT is therefore thought to have a role in oxidative mechanisms and is regarded as an early and sensitive marker of oxidative stress⁽⁷⁾.

In many prospective studies, strong relationships between GGT and alanine transferase (ALT) concentrations and incident diabetes have also been observed in non-drinkers, in individuals with normal levels of liver enzymes, independently of classical cardiovascular risk factors⁽⁸⁾.

Gamma glutamyl transferase (GGT) is a common marker of liver function and has also been associated with insulin resistance which can be a precursor to gestational diabetes and type 2 DM⁽⁹⁾. However, a strong interaction between body mass index (BMI), and GGT has been described in diabetes⁽⁹⁾. Several resembles have reported that increased GGT is independently associated with increased risk of type II diabetes in Asian and Caucasian⁽¹⁰⁾. In recent years, elevated GGT measurements have proved to be effective early warning signs of other health risks such as atherosclerosis, stroke, type 2 diabetes, kidney disease and cancer. When GGT concentrations exceeded the lowest (25%) to (35%) of normal population ranges, disease risks grow in proportion to increases in GGT. Finally Mohammad, S. K 2013⁽¹¹⁾, concluded that significant increased activity of GGT in smokers seems to support the harmful effects of cigarette smoking.

Gestational diabetes mellitus is associated with the disorder in calcium homeostasis and reduced skeletal muscle oxidative phosphorylation⁽¹²⁾. During pregnancy, requirement for calcium is increased; hence insufficient nutritional status might increase the risk of GDM. Calcium supplementation might affect metabolic profiles and oxidative stress through their effects on cell cycle regulation, activation of antioxidant enzymes and suppression of parathyroid hormone (PTH)⁽¹³⁾. Asemi Z 2014 *et al* assessed the effect of calcium and vitamin D Co supplementation on GDM in a randomized, placebo-controlled study, and they observed calcium plus vitamin D supplementation in women with GDM had beneficial effects on their metabolic profile⁽¹⁴⁾.

time gestational diabetic, 2- second time gestational diabetic and 3- type 2 DM), the Mean \pm S.E. of GGT and RSG in subgroup 3 (type 2 DM) were significantly higher than that of

subgroup 1 and 2, while there is no any significant differences of each of the calcium, and uric acid concentrations among subgroups (1, 2, and 3) of patient group.

Table (1): Mean \pm S.E. of age (year), BMI (Kg/M²), blood pressure (mm Hg), and pulse rate of study groups.

parameter	Control group Mean \pm S.E. (N=50)	GDM group Mean \pm S.E. (N=50)	t-test	P-value
Age (year)	27.8 \pm 0.85	33.4 \pm 0.74	4.96	0.002
BMI (Kg/M ²)	28.1 \pm 0.48	32.37 \pm 0.56	5.8	0.000
Systolic pressure	10.4 \pm 0.13	10.6 \pm 0.14	0.46	NS
Diastolic pressure	7.16 \pm 0.13	7.3 \pm 0.12	0.78	NS
pulse rate	81.1 \pm 0.9	82.7 \pm 0.95	1.23	NS

Table (2): Mean \pm S.E. (mg/dl) of serum concentration of GGT, RSG, Calcium, and Uric acid of study groups (control and GDM groups).

parameter	Control group Mean \pm S.E. (N=50)	GDM group Mean \pm S.E. (N=50)	t-test	P-value
GGT	6.86 \pm 0.59	11.68 \pm 0.93	4.38	0.002
RSG	91.44 \pm 2.13	229.48 \pm 10.23	13.2	0.000
Calcium	8.4 \pm 0.132	8.95 \pm 0.055	3.1	0.002
Uric acid	4.26 \pm 0.239	7.32 \pm 0.639	4.49	0.000

Note/ Results expressed as Mean \pm S.E. (P value <0.05)

Table (3): Mean \pm SEM (mg/dl) of serum concentration of GGT, RSG, Calcium, and Uric acid of study groups; Control group, and patient group (subgroups 1, 2, and3).

	Contol (N= 50)	1st dx. (N= 16)	2nd dx.(N= 16)	DM (N= 18)
Variable	Mean \pm S.E.	Mean \pm S.E.	Mean \pm S.E.	Mean \pm S.E.
GGT	6.86 \pm 0.588 ^a	7.87 \pm 0.946 ^{ab}	10.31 \pm 1.162 ^b	16.28 \pm 1.746 ^c
RSG	91.44 \pm 2.133 ^a	211.0 \pm 8.942 ^b	227.06 \pm 16.126 ^{bc}	248.06 \pm 23.076 ^c
Ca	8.39 \pm 0.132 ^a	9.10 \pm 0.094 ^b	8.92 \pm 0.129 ^b	8.86 \pm 0.051 ^b
Uric acid	4.26 \pm 0.239 ^a	8.43 \pm 1.499 ^b	7.02 \pm 0.929 ^b	6.61 \pm 0.852 ^b

Discussion:

Several biomarkers appear to be associated with the risk of gestational diabetes, such as GGT, Ca, and uric acid. In the present study, there was a significant increase in the mean serum GGT activity in GDM compared to the control subjects (P<0.002) table (2). The (mean \pm S.E.) level of serum GGT activity of the control group, and all the subgroups of GDM especially subgroup two (second time of GDM), and

subgroup 3 were significantly higher than that of control group (p< 0.002) table (3). Such results are in agreement with those obtained by Noriyuki N. *et al* 2004⁽¹⁶⁾, Serpil E, *et al* 2012⁽¹⁷⁾ and Gholamreza Y. *et al* 2012⁽¹⁸⁾. All of them reported the measuring GGT can be a sensitive method for early diagnosis and impaired glucose tolerance (IGT), metabolic syndrome (MS), and non diabetic first degree relatives (FDR) of

type 2 DM from normal condition. Because this diagnostic test is a low-cost, highly sensitive, accurate and frequently used laboratory test, the measurement is recommended as a useful marker of each of the IGT, MS, and FDR. Ibrahim, A *et al* 2012⁽¹⁹⁾ concluded that the increase at GGT level is an independent risk factor for GDM and identified as high-risk women for diagnosis of GDM. Gestational diabetes probably represents a less severe degree of hyperglycaemic tendency compared to Type 2 diabetes as evident from a 2-hour plasma glucose threshold of 140mg/dl for GDM compared to 199mg/dl threshold (typically with symptoms) for Type 2 diabetes as set by WHO. This study were done provide evidence that women who develop gestational diabetes have metabolic abnormalities even before pregnancy. It would appear that a higher GGT value is associated with a milder hyperglycaemic tendency in pregnancy in the same manner as it is associated with the development of Type 2 diabetes over the longer term⁽²⁰⁾. In a study by Serpil E *et al* 2014⁽²¹⁾, the GDM group had significantly higher mean GGT and ALT activities than the healthy controls. Similar results have been reported in patients with DM. The authors Rantala *et al* 2000⁽²²⁾ considered two mechanisms for the association between insulin resistance and GGT activity; first that insulin resistance is associated with fatty liver and this increases GGT, and second, that disturbed glucose metabolism might affect GGT more directly.

In the present study, there was a significant increase in the mean serum total calcium concentration in GDM compared to the control subjects, table (2) show the (mean \pm SD) level of serum calcium of the control group ($p < 0.000$), and all the subgroups of GDM especially subgroup one (first time of GDM) was significantly higher than that of control

group table (3). Such results are in agreement with those obtained by Yamaguchi *et al* 2011⁽²³⁾ reported significant positive correlation of serum Ca level with impaired glucose metabolism, but other results are incompatible with our results. Gregorio *et al* 1994⁽²⁴⁾ shown that diabetic patients had diminished serum Ca due to poorly controlled diabetes loss of Ca through real leaking. This is due to glucosuric-induced osmotic dieresis and is maintained by parathyroid activation. Safary K *et al* 2016⁽²⁵⁾, concluded that low urine calcium creatinine ratio and not using the calcium supplement in early pregnancy are related with GDM.

Muscle is one of the major sites responsible for insulin resistance. Calcium plays a critical role in muscle contractions and in glucose uptake after insulin binds muscle cells, also calcium influence the affinity of insulin receptor and sensitivity to insulin, whereas calcium and glucagon affect the liver plasma membrane [Ca²⁺] pump, which is thought to extrude cytosolic calcium of the cell⁽²⁶⁾.

The relatively accepted explanation is that uric acid is a substance that its production increased by the organism to counteract the increased oxidative stress associated with diabetes mellitus thus, the increase of uric acid level in diabetes mellitus representing only a defense mechanism⁽²⁷⁾. The effect of gender on uric acid level is well explained by the hormonal differences between males and females, since the estrogen have an impact on reducing the uric acid level in the blood. The association between BMI and uric acid may be explained by the fact that obesity affects urate metabolism, by decreasing urate clearance and increasing urate production⁽²⁸⁾.

Uric acid has been suggested to play a role in the pathophysiology of early onset hypertension, but the levels may tend to

dampen with age where stiffening of the aorta, activation of the renin-angiotensin system and renal vasoconstriction have a role to play⁽²⁹⁾.

Chronic inflammation and endothelial dysfunction, as observed in patients with hyperuricemia, are likely to have participation in the mechanisms through which this substance may affect renal structure and operation leading to the genesis of hypertension⁽³⁰⁾.

Finally Robert W. Powers *et al* 2006⁽³¹⁾ obtained that among women with hyperuricemia at delivery, elevations in uric acid occur early. Multiple mechanisms may contribute to increased uric acid including changes in renal function.

Conclusion:

- 1- High levels of serum GGT in GDM is caused by oxidative stress and obesity because GGT act as antioxidant and always increase in obese individuals.
- 2- Serum GGT, RSG, calcium, and uric acid levels of GDM in patient group were higher than that of control group.
- 3- Serum GGT and RSG in subgroup 3 (type 2 DM), were higher than that of subgroup 1, and 2 (GDM), while there were no any significant differences of each of the calcium, and uric acid, concentrations among subgroups.

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