Clinical Biochemistry 45 (2012) 1192–1196

Contents lists available at SciVerse ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Gamma-glutamyltransferase, alanine transaminase and aspartate transaminase levels and the diagnosis of gestational diabetes mellitus

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ARTICLE INFO

Article history:
Received 27 February 2012
Received in revised form 24 April 2012
Accepted 22 May 2012
Available online 31 May 2012

Keywords:
Gamma-glutamyltransferase
Alanine transaminases
Aspartate transaminases
Gestational diabetes
Glucose tolerance test
Glucose challenge test
Pregnancy

ABSTRACT

Objectives: To evaluate gamma-glutamyltransferase (GGT), alanine transaminases (ALT) and aspartate transaminases (AST) levels and prevalent gestational diabetes mellitus (GDM).

Design and methods: Random plasma glucose, GGT, ALT and AST and the 50-g glucose challenge test were done on antenatal women followed by diagnostic 3-point 75-g oral glucose tolerance test within two weeks. GDM was diagnosed by ADA (2011) criteria.

Results: The GDM rate was 12.2% (319/2610). Mean GGT level was higher in GDM women, 18 ± 12 vs. 16 ± 11 IU/L; P = 0.03. The risk for GDM was higher for women in the highest GGT quartile band compared to the lowest: RR 1.35 95%CI 1.0–1.8; P = 0.04. However, after adjustment for confounders, GGT was no longer associated with GDM. There was no correlation between ALT and AST levels and GDM.

Conclusions: Liver transaminases do not predict GDM in contrast to type 2 diabetes.

Introduction

A raised serum gamma glutamyltransferase (GGT)[1] level is an independent risk factor for type 2 diabetes [1]. A higher GGT concentration even within its physiological range is a sensitive and early biomarker for the development of diabetes [2] probably mediated through enhanced hepatic neoglucogenesis or early alterations of insulin secretion [3]. The association of raised GGT and development of diabetes is apparent also in young adults [4]. GGT levels in diabetic patients are independent of their hyperglycemia [5] suggesting that it is not a direct consequence of hyperglycemia. High alanine transaminase (ALT)[2] is a marker of risk for type 2 diabetes [6], can predict incident diabetes even when within the normal range [7] and remains a significant risk factor after adjustments [8]. A higher aspartate transaminase (AST)[3] level is associated with the development of impaired glucose tolerance [9] and incident diabetes [10] but its association with diabetes is not consistently demonstrated [8,9].

Women who manifested higher GGT levels when hospitalized for hyperemesis gravidarum in early pregnancy are more prone to be diagnosed as gestational diabetes (GDM)[4] later into their pregnancy [11]. In women at very risk of GDM who were undergoing diagnostic OGTT after mainly 50-g glucose challenge test (GCT)[5] screening, raised GGT level has been found to be an independent risk factor for GDM [12,13]. In the first trimester, GGT level is not independently predictive of GDM [14]. It is not established whether a higher GGT level is predictive of GDM nor is it not known whether ALT and AST is associated with GDM in the general antenatal population.

Up to 70% of women with GDM go on to develop Type 2 diabetes, with an especially rapid increase in incidence in the first five years [15]. For many of these women, GDM represents an underlying predisposition to glucose intolerance later in life unmasked by the diabetogenic effect of pregnancy. Thus we postulate that GGT, ALT and AST levels may be predictive of GDM as they are predictive of incipient Type 2 diabetes, with the diabetogenic effect of pregnancy substituting for the effect of aging.

We sought to evaluate the relationship between GGT, ALT and AST levels and the diagnosis of GDM after universal diagnostic testing in our antenatal population with a view to establishing raised liver transaminases as independent laboratory based risk factors for GDM.

Methods

Ethical oversight and approval for the study was provided by the University Malaya Medical Centre (UMMC) Medical Ethics Committee

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[1] GGT: Gamma glutamyltransferase.
[2] ALT: Alanine transaminase.
[3] AST: Aspartate transaminase.
[4] GDM: Gestational diabetes mellitus.
[5] GCT: 50-g glucose challenge test.

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doi:10.1016/j.clinbiochem.2012.05.025

(approval no. 642.12, dated 19 March 2008) for the UMMC Liver Transaminases for Gestational Diabetes Screening and Diagnosis Study. The study recruited from 3 August 2009 to 28 Feb 2011. Written consent was obtained from subjects. The study conformed to the provisions of the Helsinki Declaration on human studies (revised in Edinburg in 2000).

The study was done in our city-based university hospital conducting over 5000 deliveries per year. Our general antenatal population was at high risk for GDM with an incidence of at least 11.4% after universal 50-g GCT screening followed by diagnostic testing with the 75-g oral glucose tolerance test (OGTT) [16].[6] For this study, we aimed to recruit 3000 women based on the funding obtained.

Women who attended for their first antenatal care appointment were identified by clinic staff. Women not known to have diabetes mellitus or gestational diabetes at this point were approached and consented if they agree to take part. The study required additional blood to be drawn for random plasma glucose, GGT, ALT and AST together with routine antenatal blood tests. The 50-g GCT was then performed (hence another blood sample was drawn for plasma glucose at 1 h) without consideration of recent oral intake. A questionnaire on basic demographics, timing and quantification of recent oral intake and tolerance towards the GCT was also distributed to participants to answer and return at end of the clinic visit.

All participants were given instruction on the preparation for a 3-point 75-g OGTT. Diagnostic OGTT was performed as specified by the World Health Organisation (WHO) [17]. We opted to apply the 3-point rather than 2-point OGTT to maximise data harvesting and future proofing as the diagnostic criteria for the OGTT seemed to be in a state of flux following publication of the HAPO study [18]. An appointment for the OGTT was then made for all participants within the next two weeks at their convenience irrespective of their initial test results. Participants who did not attend their OGTT appointment were contacted and given another if they agreed. Postnatal OGTT six or more weeks after delivery is planned but only for women diagnosed as GDM. Pregnancy outcome is to be retrieved from case notes after delivery.

All blood samples obtained for the purpose of the study were sent immediately to our hospital's clinical chemistry laboratory for standard processing and reporting. Our hospital laboratory used Dimension Vista® 1500 Intelligent Lab System (Siemens AG, Germany) to analyse the samples. In the period July to Dec 2011, our laboratory reported (low test value) precisions of 2.2%, 3.1%, 3.3%, and 6.9% and (high test value) precisions of 2.2%, 1.9%, 2.0% and 2.3 for glucose, GGT, ALT and AST respectively in internal quality control analyses. All results for the random plasma glucose, GGT, AST, ALT, 50-g GCT and 3-point 75-g OGTT were promptly made available to care providers through the hospital's computerised laboratory reporting service as they became ready.

In our hospital, the standard antenatal care for the identification of GDM was the two-step screen, using the 50-g GCT with screen positive threshold set at ≥7.2 mmol/L followed by diagnostic 2-point75-g OGTT for those screened positive. The GCT was performed at the initial hospital visit as the mean gestational age of our patients at the first visit was about 28 weeks [16] in conjunction with other routine antenatal blood investigations. Women who did not wish to participate in our study were offered this routine screening. In our hospital, diagnosis of GDM after the 2-point 75-g OGTT was in accordance with WHO (1999) criteria (fasted plasma glucose ≥7.0 and/or 2-hour plasma glucose ≥7.8 mmol/L) [17].

All women diagnosed as GDM were referred to our joint clinic for diabetes care in pregnancy, provided by a team of obstetricians, diabetes physicians and nurses and nutritionists for their ongoing care.

[6] OGTT: 75-g glucose tolerance test.

For the purpose of this report, we restricted the study population to those participants whose GGT, ALT, AST as well as the 3-point OGTT results were complete. We excluded women with liver disease (e.g. Hepatitis B carrier status). We applied the American Diabetes Association (2011) position statement on the interpretation of the 3-point 75-g OGTT with GDM diagnostic criteria fulfilled if one or more point readings were at or beyond plasma glucose cut-offs of ≥5.1 mmol/ (fasted), ≥ 10.0 mmol/L (1-hour) and ≥8.5 mmol/L (2-hour) [19].

Data were entered into a statistical software package SPSS version 15 (SPSS Inc., Chicago IL). We also used MedCalc software (Mariakerke, Belgium) for Chi Square for Trend analysis. We determined the quartile cut-offs values for GGT, ALT and AST for the study population with a view to assessing trend (using the Chi Square for Trend test) for diagnosis of GDM versus quartile values of the transaminases and to assess relative risk for GDM utilising the bottom quartile as the referent value. We plotted the receiver operator characteristic curves for transaminases' values against diagnosis of GDM to obtain the area under the curve. We also evaluated various characteristics including the random plasma glucose and GCT values in additional to the transaminases levels in women with and without GDM using the Student *t* test, Chi Square test or the Mann Whitney *U* test in bivariate analysis to establish significant associations of these characteristics with GDM. The characteristics with significant association ($P<0.05$) to GDM on bivariate analyses were included in a multivariable logistic regression analysis model to establish independent associations. $P<0.05$ in any 2-sided tests was considered statistically significant.

Results

3094 women were consented for the study. Fourteen women were later excluded due to liver disorders, mainly Hepatitis B infection found on routine antenatal screening. A number of 2-point OGTT were done for participants due principally to confusion with women on standard care as OGTTs for both groups were performed in the same clinic setting. Only 2610 women had complete liver transaminases and 3-point OGTT results and they formed the study population.

Of the women who did and did not attend for OGTT following their GCT, 1000/2758 (36.3%) vs. 29/287 (10.1%) respectively had a positive GCT screen (with 1- hour plasma glucose ≥7.2 mmol/L); $P<0.001$. This is expected as participants with a positive GCT screen as well as their providers were jointly aware of the GCT result and would have made a greater effort towards a diagnostic OGTT.

Receiver operator characteristic curve analysis for transaminases levels versus GDM showed area under the curve of 0.54 ($P=0.021$) for GGT, 0.509 ($P=0.61$) for ALT and 0.475 ($P=0.147$) for AST indicating a statistically significant but rather weak practical utility for GGT as a marker for GDM but none at all for ALT and AST.

The demographics of the 2610 women stratified according to their GDM status are shown in Table 1. On bivariate analysis, women with GDM compared to those without were older, of higher parity, heavier and with higher body mass index (BMI) and had higher mean systolic and diastolic blood pressure. Biochemical characteristics are shown in Table 2. Random plasma glucose, GCT and GGT levels are higher in women with GDM but mean ALT and ALT levels were not different. Chi Square for trend analysis after banding transaminases levels into quartiles showed a significant result for GGT but not for ALT or AST. The relative risk (RR) of GDM for the highest GGT quartile compared to the lowest GGT quartile RR 1.35 95% CI 1.02–1.80) was significantly higher ($P=0.039$).

Multivariable logistic regression analysis (Table 3) incorporating age, body weight, BMI, parity, systolic and diastolic blood pressure, random plasma glucose and 1-hour GCT plasma glucose as continuous variables and GGT quartiles (lowest quartile as referent) and ethnicity (Malay as referent) as categorical variables was performed.