Three-year increase of gamma-glutamyltransferase level and development of type 2 diabetes in middle-aged men and women: the D.E.S.I.R. cohort.

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Abstract

Aims/Hypothesis—Among hepatic markers, gamma-glutamyltransferase (GGT) is the main predictor for the development of type 2 diabetes, but there is no data on GGT change and type 2 diabetes incidence.

Methods—Data at baseline and at three years from the D.E.S.I.R. cohort were used: 2071 men and 2130 women without baseline diabetes.

Results—Change in GGT level was correlated with changes in markers of insulin-resistance (fasting insulin, HOMA index) as well as with elements of the metabolic syndrome: fasting glucose, central obesity, triglycerides, systolic and diastolic blood pressure. The three-year increase in GGT was associated with incident type 2 diabetes, in both sexes, after adjusting for age and baseline GGT. After further adjustment for baseline confounding factors including alanine-aminotransferase, alcohol intake, overall and central obesity, the odds ratios (95% CI) for incident type 2 diabetes associated with an increase compared to a decrease in GGT level were 2.54 (1.38-4.68) in men ($p<0.003$) and 2.78 (1.20-6.42) in women ($p<0.02$). These associations were slightly attenuated after adjusting for the 3-year change in BMI, alcohol consumption, fasting insulin: 2.49 (1.28-4.86) in men and 2.53 (1.01-6.40) in women. This relationship was not dependent on intra-individual variability.

Conclusions—An increase in GGT level over time, even when GGT is in the normal range, is correlated with increasing insulin resistance and is associated with a risk of incident type 2 diabetes in both sexes, independently of baseline GGT, which is itself a diabetes risk factor.

Keywords GGT, insulin resistance, sex, Type 2 diabetes

Abbreviations: ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; GGT, gamma-glutamyltransferase; FPG, fasting plasma glucose; HOMA, homeostasis model insulin resistance assessment; OR, odds ratio

Introduction

Since the original published data in British men [1], recent prospective studies [2-7] have confirmed a significant association between gamma-glutamyltransferase level (GGT) and the incidence of type 2 diabetes, in both sexes and in populations from different countries. This association is independent of classical markers of diabetes: age, BMI and also of other factors associated with GGT activity such as excessive alcohol consumption and liver diseases [2-7]. Furthermore when GGT was tested along with other hepatic markers such as alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), bilirubin and alkaline phosphatase, GGT was the main predictor of tType 2 diabetes [5,7]. It has also been shown in men that GGT was a significant marker of the metabolic syndrome [5]. Few data have been published on the longitudinal change in GGT; and they showed a strong association between an increase in GGT and an increase in BMI, in both sexes but other factors were associated differently in men and in women [8].

Our aim was to examine the relationship between GGT change and the change in factors associated with type 2 diabetes (glycaemia, overall and central obesity), with GGT level (age, alcohol consumption, smoking habits), and with insulin resistance markers (fasting insulin, HOMA). We tested also studied whether a change in GGT was associated with the incidentce of type 2 diabetes, and if so, whether this association was independently of risk markers of for diabetes and insulin resistance.

Subjects and methods

Study population

This analysis used data from the inclusion and the three-year follow-up examinations of the D.E.S.I.R. cohort study (Data from Epidemiological Study on the Insulin Resistance syndrome): a longitudinal study that aims to clarify the natural history of the insulin resistance syndrome [7]. Among the 5212 volunteers who participanted in the cohort, the 2071 men and 2130 women without diabetes at baseline were included in this analysis, as previously described [7].

Statistical analysis

Relations between the three-year change in GGT and baseline and three-year changes values in anthropometric and metabolic variables were examined by Spearman correlation coefficients.

The associations between the risk of incident type 2 diabetes over three years and the three-year variation in GGT (decrease (<0) or an increase (≥0)) were analysed separately in men and women, using logistic regression analysis. This comparison was equivalent to comparing those above the higher tertile of GGT change with those below. Covariates used were:

1- Baseline age (years), GGT (in quartiles), ALT (in quartiles), BMI, smoking habits (never, former, current), physical activity (4 levels), alcohol intake (gram/day), fasting insulin (μU/ml) and glucose (mmol/l). Variables not normally distributed were log transformed.

2- Three-year changes in BMI, alcohol intake and fasting insulin.

For each covariate, interactions with the three-year change in GGT were tested by likelihood ratio tests, comparing models with and without the interactions terms.

According to the reported coefficients ofAs the intra-individual biological variability of GGT of is reported to be 12.2% [9], we repeated the analyses by comparing participants with an increase of GGT (> +5U/L) or a stable GGT (-5 to +5U/L) to those with a decrease (<-
5U/L).

The SAS statistical program, version 8.0, was used in all analyses.

Results

Over the three years, the mean GGT level decreased by 3.0 IU/l in men and 2.2 IU/l in women. These three-year GGT changes were highly and negatively correlated with baseline values of GGT and ALT in both sexes, but not with alcohol intake (Table 1). GGT change was positively correlated with the change in ALT, fasting glucose, central (WHR) or overall obesity (BMI), insulin resistance (evaluated by fasting insulin, HOMA), each parameter of the metabolic syndrome (excepting HDL-cholesterol change) as well as with the change in alcohol intake.

Over the three years, 89 subjects developed diabetes: 2.8% in men, 1.4% in women (Table 2). Participants with an increase in GGT had an increased risk to develop type 2 diabetes compared to those with a decrease in GGT, with odds ratios (OR) of 1.77 (95%CI: 1.04-3.02) in men and 3.28 (1.57-6.86) in women, after adjusting for age and baseline GGT. Further adjustment for baseline confounders (BMI, ALT, smoking habits, alcohol intake, physical activity, fasting insulin and glucose) slightly modified this association, differently in men and women, with an ORs of 2.54 (1.38-4.68) in men and 2.78 (1.20-6.42) in women. None of the tested interactions were significant.

When the three-year change in BMI, fasting insulin or alcohol intake were added separately or all together into the latter model, adjusted on all baseline values (Table 2), the association between increased GGT and type 2 diabetes incidence remained significant with an OR of 2.49 (1.28-4.86) in men and 2.53 (1.01-6.40) in women. The ORs were similar when fasting insulin was replaced by the HOMA index or BMI by WHR or waist circumference (data not shown). This comparison was equivalent to comparing those above the higher tertile of GGT change with those below. When we divided the GGT change in three groups. The ORs to develop type 2 diabetes, adjusted on the same covariates, comparing the participants with an increase in GGT (>+5U/L) or a stable GGT (-5 to +5U/L) to those with a decrease (<-5U/L) were respectively 3.03 (1.47-6.25) in men, 2.69 (0.84-8.59) in women, and 1.59 (0.74-3.43) in men, 1.67 (0.54-5.15) in women.

Discussion

In this study, an increase in GGT over three years was positively associated with the incidence of type 2 diabetes in both sexes. This association was independent of baseline values of confounding factors including GGT, age, BMI, fasting glucose and insulin. Among baseline hepatic markers, GGT was the main risk factor for type 2 diabetes in this population [7] as well as in a population of Japanese men [5]. Our study is the first to show a correlation between the change in GGT and the change in insulin resistance markers (fasting insulin, HOMA). The HOMA index is a well-validated method used to measure insulin resistance that showed a good correlation (0.58 to 0.88) with reference techniques [10] such as the euglycaemic clamp. The change in GGT was more associated with change in ALT than with the change in insulin resistance markers or obesity (central or overall). However, the risk of type 2 diabetes with change in GGT, was little modified, after adjustment for changes in

these parameters, despite the significant correlations observed with the change in each of these parameters.

Our data support the hypothesis that GGT could be a marker of hepatic steatosis or visceral obesity. GGT change was correlated with the change in ALT (the main marker of Non Alcoholic Steato-Hepatitis, NASH) and was also correlated with changes in insulin resistance markers and with obesity indexes. However, change in GGT was a risk factor for type 2 diabetes, independently of these markers, and ORs were similar after adjustment.

The main limitation of our study is that both type 2 diabetes incidence and the change in GGT were assessed over the same three-year period. Type 2 diabetes was diagnosed before or at the same time as the three-year assessment of GGT. The observed association between the incidence of type 2 diabetes and GGT change could be explained by either the fact that diabetes status caused a GGT increase as shown in previous cross-sectional studies [5], where diabetic patients had a higher GGT than non-diabetic patients, or by the fact that the increase in GGT preceded or predicted the onset of diabetes. However, the GGT change was significantly associated with the change in insulin resistance in the whole population and not only in diabetic subjects. This association with insulin resistance change is at least partially supportive of the hypothesis that the change in GGT preceded diabetes onset, as insulin is predictive of diabetes incidence.

This study has two limitations due to the selection of the participants. Firstly they were volunteers and certainly not representative of the general population, with an under-representation of people with chronic diseases [7]; secondly, 13% of the participants were not followed for the three years – and they had higher baseline GGT and ALT levels, but fasting glucose was similar [7]. Nevertheless this selection

bias would have a limited impact on the association that clearly exists in this population.

The intra-individual variability of the GGT measurement could also result in a classification bias. Limited changes in GGT over time could be more related to this variability than to a real GGT change. Nevertheless the ORs to develop diabetes, comparing participants with a GGT increase larger than intra-individual variability with those with a decrease larger than the intra-individual variability were similar and the association was also significant. . Thus the intra-individual variability, including measurement error, cannot explain the reported association between GGT change and type 2 diabetes incidence.

These results, observed in middle-aged adults, support the hypothesis that an increase in GGT over time, even within the normal range, is associated with a change of insulin resistance markers and with a higher incidence of type 2 diabetes in both sexes, independently of baseline GGT. This association was independent of known confounding factors, of GGT and of the classical diabetes risk markers. GGT is a universally standardized and available measurement that could be a clinical marker of the insulin resistance state and its changes.

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Table 1 Spearman correlation coefficients between the change in GGT level over three years with baseline and three-year changes in covariates. The D.E.S.I.R. study

	GGT change over three years			
	Men		Women	
	n=2071	*P* value	n=2130	*P* value
Baseline characteristics				
Age (years)	-0.05	0.02	<0.01	0.97
GGT (IU/l)	-0.28	0.0001	-0.27	0.0001
ALT (IU/l)	-0.23	0.0001	-0.14	0.0001
AST (IU/l)	-0.13	0.0001	-0.02	0.21
Bilirubin (mg/ml)	-0.01	0.0001	<0.01	0.94
Alcohol intake (gram/day)	-0.03	0.14	<-0.01	0.82
BMI (kg/m^2)	-0.08	0.0003	0.02	0.30
Waist hip ratio	-0.10	0.0001	-0.01	0.77
Fasting Insulin (μU/ml)	-0.12	0.0001	-0.05	0.02
HOMA[a]	-0.13	0.0001	-0.06	0.003
Fasting Plasma Glucose (mmol/l)	-0.11	0.0001	-0.09	0.0001
Triglycerides (mmol/l)	-0.16	0.0001	-0.05	0.02
HDL-Cholesterol (mmol/l)	+0.04	0.07	-0.03	0.08
Systolic Blood Pressure (mm Hg)	-0.07	0.0006	-0.01	0.63
Diastolic Blood Pressure (mm Hg)	-0.13	0.0001	-0.03	0.12
Changes over three years				
ALT (IU/l)	0.43	0.0001	0.30	0.0001
Alcohol intake (gram/day)	0.09	0.0001	0.06	0.004
BMI (kg/m^2)	0.12	0.0001	0.15	0.0001
Waist hip ratio	0.12	0.0001	0.07	0.0008
Fasting Insulin (μU/ml)	0.14	0.0001	0.12	0.0001
HOMA*	0.15	0.0001	0.14	0.0001
Fasting Glucose (mmol/l)	0.11	0.0001	0.14	0.0001
Triglycerides (mmol/l)	0.21	0.0001	0.14	0.0001
HDL-Cholesterol (mmol/l)	0.01	0.75	0.01	0.83
Systolic Blood Pressure (mm Hg)	0.09	0.0001	0.04	0.07
Diastolic Blood Pressure (mm Hg)	0.13	0.0001	0.07	0.0005

Data are Spearman correlation coefficients
[a]HOMA for homeostasis model assessment

Table 2 Odds ratios (95% confidence intervals) of three-year incident diabetes for a three-year increase in GGT, adjusted on baseline values and three-year changes in covariates. The D.E.S.I.R. study

	GGT level change		*P value*
	Decrease	Increase	
Men			
Incident cases of diabetes/number of subjects	32/1312	27/759	
Model A	1	1.77 (1.04-3.02)	0.04
Model B	1	2.54 (1.38-4.68)	0.003
Model B+ BMI change	1	2.44 (1.31-4.54)	0.005
Model B+ alcohol intake change	1	2.57 (1.39-4.75)	0.003
Model B+ fasting insulin change	1	2.48 (1.28-4.81)	0.007
Model B+BMI, alcohol, insulin change	1	2.49 (1.28-4.86)	0.008
Women			
Incident cases of diabetes/number of subjects	13/1487	17/643	
Model A	1	3.28 (1.57-6.86)	0.002
Model B	1	2.78 (1.20-6.42)	0.02
Model B+ BMI change	1	2.42 (1.01-5.84)	0.05
Model B+ alcohol intake change	1	2.87 (1.24-6.67)	0.02
Model B+ fasting insulin change	1	2.82 (1.17-6.76)	0.03
Model B+BMI, alcohol, insulin change	1	2.53 (1.01-6.40)	0.05

Model A: adjusted for age and baseline GGT level

Model B: model A with additional adjustment on baseline alcohol intake, physical activity, smoking habits, ALT, BMI, fasting insulin and fasting glucose