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ARTICLE

Risk factors for incident type 2 diabetes in individuals with a BMI of <27 kg/m^2: the role of γ-glutamyltransferase. Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR)

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Abstract
Aims/hypothesis Risk factors for incident type 2 diabetes, in particular, hepatic markers, have rarely been studied in leaner individuals. We aimed to identify the metabolic and hepatic markers associated with incident diabetes in men and women with a BMI of <27 kg/m^2 and to compare them with those in individuals with a BMI of ≥27 kg/m^2.
Methods Risk factors for 9 year incident diabetes were compared in the French Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort. Comparisons were made between the 2,947 participants with a BMI of <27 kg/m^2 and the 879 with a BMI of ≥27 kg/m^2.
Results There were 92 incident cases of diabetes in individuals with a BMI of <27 kg/m^2 and 111 in those with a BMI of ≥27 kg/m^2. Among those who were not markedly overweight, classical biological markers were associated with 9 year incident diabetes, glycaemia being the strongest predictor. γ-Glutamyltransferase (GGT), either considered as a continuous variable or at levels ≥20 U/l, was associated with incident diabetes, with a stronger effect in the BMI <27 kg/m^2 group: OR 1.59 (95% CI 1.29–1.97, p<0.001) in comparison with OR 1.07 (95% CI 0.82–1.38, p=0.63) for those with a BMI of ≥27 kg/m^2 (results after adjustment for alcohol intake, alanine aminotransferase, waist circumference and the HOMA insulin resistance index).
Conclusions/interpretation In individuals with a BMI of <27 kg/m^2, GGT was the strongest predictor of diabetes after fasting hyperglycaemia. This association with incident diabetes remained after adjustment for conventional markers of insulin resistance, suggesting potential interactions between GGT, enhanced hepatic neoglucogenesis and/or early alterations of insulin secretion.

Keywords BMI · Diabetes · γ-glutamyltransferase · Liver · Risk factors

Abbreviations

ALT	Alanine aminotransferase
DESIR	Data from an Epidemiological Study on the Insulin Resistance Syndrome
GGT	γ-Glutamyltransferase
HOMA-IR	HOMA insulin resistance index
NAFLD	Non-alcoholic fatty liver disease

A full list of members of the DESIR Study Group can be found in the Electronic supplementary material.

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Introduction

The prevention of type 2 diabetes remains a major public health issue worldwide. Obesity and increased abdominal adiposity are key risk factors for the development of type 2 diabetes in people with impaired glucose tolerance [1, 2], as well as in the general population [3–5]. Previous trials investigating prevention strategies have included people with impaired glucose metabolism and increased BMI [3].

In Europe, and especially in France, the prevalence of obesity is lower than in North America and type 2 diabetes among people with a BMI of <27 kg/m^2 is quite common [4]. However, the clinical and biological determinants of new-onset type 2 diabetes among individuals who are not markedly overweight or obese remain poorly understood. Previous studies assessing risk factors for type 2 diabetes in the general population did not perform subgroup analyses according to BMI [5, 6]. The majority of non-obese people at high risk of type 2 diabetes are not included in prevention programmes, as it is difficult to identify them.

The aim of the present study was to determine the main type 2 diabetes risk factors among persons with a BMI of <27 kg/m^2 in the large prospective study, Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) [7, 8]. In this cohort, the proportion of participants with obesity is lower than in most studies on incident diabetes [7, 8]. We examined the clinical and biological determinants of new-onset type 2 diabetes according to BMI at baseline; in particular, in participants with a BMI of <27 kg/m^2 and in those with normal body weight (BMI <25 kg/m^2) at baseline.

Methods

Study population We studied men and women aged 30 to 64 years who participated in the DESIR study, a 9 year follow-up study that aims to clarify the development of the insulin resistance syndrome and type 2 diabetes [7, 8]. Participants were recruited from volunteers offered free periodic health examinations by the French Social Security in ten health examination centres in western France. All participants signed an informed consent document and the protocol was approved by an ethics committee.

Incident cases of diabetes were identified as participants found to be undergoing treatment for diabetes or participants with fasting plasma glucose ≥7.0 mmol/l at one of the three 3 yearly follow-up examinations. After exclusion of individuals with diabetes at baseline, 1,865 men and 1,962 women were studied.

Measures Two measures of blood pressure using a mercury sphygmomanometer were taken in a supine position after 5 min rest; mean values were used. Weight and height of participants were measured in light clothing and a tape measure was used to measure waist circumference at the smallest circumference between the lower ribs and the iliac crests. The examining physician also noted any family history of diabetes and hypertension; smoking habits, alcohol intake, physical activity and treatment for diabetes, hypertension and lipids were recorded on an auto-questionnaire.

All biochemical measurements were from one of four health-centre laboratories located in France at Blois, Chartres, La Riche or Orléans. Fasting plasma glucose was measured by the glucose-oxidase method with fluoro-oxalated plasma using various devices (Technicon RA100; Bayer Diagnostics, Puteaux, France; Specific or Delta devices; Konelab, Evry, France). Total cholesterol, HDL-cholesterol and triacylglycerol were assayed by Dax 24 (Bayer Diagnostics) or Kone devices (Konelab). γ-Glutamyltransferase (GGT) and alanine aminotransferase (ALT) activities were measured at 37°C with an automatic analyser (Technicon Dax 24; Bayer Diagnostics; or Lab 20 or Delta 60i; Konelab).

Statistical analysis All analyses were performed using R Version 2.6.2 (Free Software Foundation, Boston, MA, USA) and a two-sided value of $p<0.05$ was considered to be statistically significant. Skewed variables (GGT, ALT, triacylglycerol, HDL-cholesterol, insulinaemia) were log-transformed before analysis. The HOMA insulin resistance index (HOMA-IR) was calculated as described previously [9]. Student's t and χ^2 tests were used to compare baseline characteristics.

The logistic model was used to determine standardised ORs with Wald 95% CIs and p values for incident diabetes, conditioned on baseline BMI categories and adjusted for family history of diabetes, sex, baseline age, alcohol intake, current smoking, physical activity, fasting glycaemia, waist circumference, HOMA-IR and 9 year change in weight.

The median BMI of individuals with incident diabetes at 9 years follow-up was 27.4 kg/m^2. Interactions with sex were tested for the prediction of diabetes, with each variable in the two BMI subgroups, i.e. <27 kg/m^2 and ≥27 kg/m^2. Of the 18 interactions tested, only HDL-cholesterol in the BMI <27 kg/m^2 subgroup was found to be significantly more predictive in women, which might be due to chance. Moreover, only 23 new-onset cases of diabetes occurred in women with a BMI of <27 kg/m^2. We concluded that separate analyses in men and women were not necessary, and we adjusted for sex. Interactions were also tested between BMI subgroups and predictors of incident diabetes.

GGT was analysed as a continuous variable and also studied in classes, i.e. <20 U/l, 20 to 40 U/l and>40 U/l in

the entire population, as well as separately in participants with moderate alcohol intake (<30 g/day for men, <20 g/day for women).

Results

Each baseline metabolic marker was significantly higher (or lower for HDL-cholesterol) in participants with a BMI of ≥27 kg/m^2 than in those with a lower BMI (Table 1). At the end of the 9 year follow-up, 92 incident cases of diabetes (69 men, 23 women) were observed in the lower BMI group at baseline and 111 cases (71 men, 40 women) in the higher BMI group. There were 52 incident cases of diabetes (39 men, 13 women) among those with a BMI of <25 kg/m^2 at baseline. Overall, among participants in the entire cohort who developed diabetes, 45% had a BMI of <27 kg/m^2 and 26% a BMI of <25 kg/m^2 at baseline.

Fasting glycaemia, GGT, ALT, triacylglycerol, waist circumference and systolic blood pressure were significantly associated with the incidence of diabetes among individuals with a BMI of <27 kg/m^2 and in those with a BMI of ≥27 kg/m^2 at baseline after adjustment for family history of diabetes, sex, baseline age, current smoking, alcohol intake, physical activity and 9 year weight change. Fasting glycaemia was associated with the highest standardised OR. After further adjusting for fasting glycaemia and waist circumference, GGT was associated with the highest OR per 1 SD change in the BMI <27 kg/m^2 group: 1.59 (95% CI 1.29–1.97) (Table 2). In contrast, GGT was not associated with incident diabetes in those with a BMI of ≥27 kg/m^2 and the interaction with BMI group was significant (p<0.008). For the other risk factors, ALT and triacylglycerol, ORs were not significantly different between the two BMI categories, whereas HDL-cholesterol, insulinaemia and the HOMA-IR index were significantly related with incident diabetes in those with a BMI of ≥27 kg/m^2 only (Table 2). There was no significant interaction between GGT and sex for the risk of incident diabetes.

The significant association between GGT and incident diabetes persisted after further adjustment for ALT (data not shown), or for the HOMA-IR index and was stronger after excluding the heavier alcohol drinkers, i.e. those who

Table 1 Characteristics of participants according to BMI at baseline. The DESIR Study

Variable	BMI <27kg/m^2	BMI ≥27kg/m^2	p value
Participants (n)			
All	2,947	879	
Men	1,370	494	<0.0001
Women	1,577	395	
Incident cases of diabetes (n)			
All	92	111	
Men	69	71	<0.091
Women	23	40	
Current smoking, % (n)	19.5 (575)	17.5 (154)	0.28
Physical activity[a]	1 (0.5, 1.25)	0.75 (0.5, 1.25)	<0.0001
9 year weight gain (kg)	2.0 (0, 5)	2.0 (−1, 6)	0.80
Fasting plasma glycaemia (mmol/l)	5.19 (4.87, 5.54)	5.49 (5.11, 5.86)	<0.0001
GGT			
All (U/l)	19.7 (14.7, 29.7)	29.4 (19.7, 46.2)	<0.0001
<20 U/l, % (n)	53.2 (1,569)	28.6 (251)	<0.0001
20–40 U/l, % (n)	31.7 (934)	39 (343)	
>40 U/l, % (n)	15.1 (445)	32.4 (285)	
ALT (U/l)	19.9 (15.0, 26.9)	26.8 (19.9, 37.7)	<0.0001
Triacylglycerol (mmol/l)	0.88 (0.63, 1.21)	1.25 (0.90, 1.82)	<0.0001
HDL-cholesterol (mmol/l)	1.65 (1.39, 1.96)	1.44 (1.19, 1.70)	<0.0001
Fasting insulinaemia (pmol/l)	35.7 (26.7, 48.0)	56.5 (42.4, 79.5)	<0.0001
HOMA-IR	1.19 (0.86, 1.64)	2.03 (1.46, 2.88)	<0.0001
Waist circumference (cm)			<0.0001
Men	86 (81, 90)	99 (95, 103)	
Women	72 (68, 78)	90 (86, 95)	
Systolic BP (mmHg)	128 (120, 135)	138 (128, 145)	<0.0001

Data are expressed as median (1st, 3rd quartile) unless stated otherwise

[a] 0, none; 1, moderate; 2, intensive

Table 2 Standardised odds ratios for 9 year incident type 2 diabetes per 1 SD change of risk factors. The DESIR Study

Variable	BMI <27kg/m^2		BMI ≥27kg/m^2		p value for interaction with BMI groups
	OR (95% CI)	p value	OR (95% CI)	p value	
GGT	1.59 (1.29–1.97)	2.10^{-5}	1.07 (0.82–1.38)	0.63	0.008
ALT	1.34 (1.08–1.68)	0.009	1.37 (1.06–1.77)	0.018	0.63
Triacylglycerol	1.34 (1.06–1.69)	0.014	1.41 (1.10–1.81)	0.0067	0.94
HDL-cholesterol	0.89 (0.68–1.15)	0.37	0.77 (0.58–1.02)	0.064	0.79
Insulinaemia	1.12 (0.87–1.43)	0.38	1.39 (1.07–1.80)	0.012	0.39
HOMA-IR	1.15 (0.97–1.37)	0.12	1.24 (1.01–1.52)	0.045	0.46

ORs (95% CIs) are adjusted for family history of diabetes, sex, baseline age, alcohol intake, current smoking, physical activity, glycaemia, waist circumference and 9 year weight change

consumed, at baseline, more than 30 g/day (men) and 20 g/day (women) (Table 3). GGT was not significantly related with incident diabetes in the heavier alcohol drinkers in either of the BMI categories for any of the multivariate models tested (data not shown).

Further, GGT (considered as a continuous variable) was the only marker significantly associated with incident diabetes among participants with a BMI of <25 kg/m^2 in the multivariate models (Model 2, OR 1.52, 95% CI 1.15–2.00, p=0.003).

Table 3 Odds ratios for 9 year incident type 2 diabetes according to GGT levels in all participants and in moderate drinkers (<30 g/day for men and <20 g/day for women). The DESIR Study

Model	GGT <20 U/l	GGT 20 – 40 U/l	p value[a]	GGT ≥40 U/l	p value[a]
Model 1[b]					
All participants (n=3,826)					
BMI <27 kg/m^2 (n=2,947)	1	3.04 (1.59–5.81)	0.0008	5.21 (2.63–10.3)	<0.0001
BMI ≥27 kg/m^2 (n=879)	1	1.81 (0.93–3.50)	0.079	2.62 (1.32–5.20)	0.006
Moderate drinkers (n=2,839)					
BMI <27 kg/m^2 (n=2,217)	1	4.30 (1.90–9.75)	0.0005	7.34 (3.13–17.2)	<0.0001
BMI ≥27 kg/m^2 (n=622)	1	1.78 (0.95–3.72)	0.13	2.60 (1.20–5.65)	0.016
Model 2[c]					
All participants (n=3,826)					
BMI <27 kg/m^2 (n=2,947)	1	2.55 (1.30–5.00)	0.0063	4.10 (2.00–8.43)	0.0001
BMI ≥27 kg/m^2 (n=879)	1	1.48 (0.72–3.72)	0.29	1.69 (0.78–3.67)	0.18
Moderate drinkers (n=2,839)					
BMI <27 kg/m^2 (n=2,217)	1	3.46 (1.48–8.10)	0.0042	5.70 (2.30–14.1)	0.0002
BMI ≥27 kg/m^2 (n=622)	1	1.65 (0.73–3.70)	0.23	1.93 (0.80–4.62)	0.14
Model 3[d]					
All participants (n=3,826)					
BMI <27 kg/m^2 (n=2,947)	1	2.74 (1.47–5.41)	0.0025	4.37 (2.15–8.72)	<0.0001
BMI ≥27 kg/m^2 (n=879)	1	1.82 (0.92–3.59)	0.085	2.26 (1.10–4.63)	0.026
Moderate drinkers (n=2,839)					
BMI <27 kg/m^2 (n=2,217)	1	3.80 (1.66–8.67)	0.0015	5.98 (2.49–14.33)	<0.0001
BMI ≥27 kg/m^2 (n=622)	1	1.75 (0.83–3.69)	0.14	2.30 (1.03–5.10)	0.041

Values are ORs (95% CIs)

[a] In comparison with the GGT <20 U/l group

[b] Adjusted for family history of diabetes, sex, baseline age, alcohol intake, current smoking, physical activity, waist circumference and 9 year weight change

[c] As Model 1 with additional adjustment for fasting glycaemia

[d] As Model 2 with adjustment for HOMA-IR index instead of fasting glycaemia

Discussion

The main finding of this study is that GGT and ALT activities were associated with the risk of 9 year incident diabetes in men and women with a BMI of <27 kg/m^2. A moderate elevation of GGT concentration within the normal range appears to be a strong risk marker for the subsequent onset of diabetes, independently of classical risk factors for diabetes or other indicators of insulin resistance such as abdominal adiposity or the HOMA-IR index.

In our study, conventional metabolic risk markers validated in other populations [6] were also predictive of future diabetes in those with a BMI of <27 kg/m^2. As expected, fasting glycaemia was associated with the highest standardised OR for incident diabetes, as shown in previous reports [3, 5, 6, 8]. Similarly, waist circumference was a strong risk factor for new-onset type 2 diabetes, regardless of initial BMI. This is in agreement with previous studies [10, 11] and emphasises the importance of abdominal adiposity in the pathophysiology of insulin resistance and type 2 diabetes.

To our knowledge, this study is the first to have specifically determined risk factors for incident diabetes among individuals without excessive body weight at baseline. The DESIR cohort had 77% of participants with a baseline BMI of <27 kg/m^2, with 45% of the incident cases of diabetes coming from this group. Thus screening for and prevention of type 2 diabetes should not be restricted to obese individuals. Indeed, the identification of reliable risk markers among people of normal weight is very relevant.

Recent prospective studies have confirmed a significant association between GGT activity and the incidence of type 2 diabetes in both sexes and in various populations, including the DESIR cohort [12–18].

In the present study, the association between GGT and risk of type 2 diabetes appeared to be independent of insulinaemia or the HOMA-IR index, suggesting alternative underlying mechanisms. Diabetes status has been previously associated with increased GGT levels [16]. However, the correlation between GGT and fasting glycaemia was weak in our study. In addition, the relationship between GGT or ALT levels and the risk of diabetes persisted after accounting for fasting glycaemia, suggesting that the elevation of these liver markers could not be seen as a simple consequence of hyperglycaemia.

We observed that the association between GGT and the risk of incident diabetes is enhanced among persons with a BMI of <27 kg/m^2, in contrast to ALT, which was more strongly related with diabetes risk among the more obese participants. These findings differ from a previous cross-sectional report, which, in a large sample of the US population, showed a stronger association between elevated plasma GGT levels and the risk of prevalent diabetes in persons with obesity than in those with a lower BMI [19]. However, as this study was not prospective and considered only newly recognised diabetes, the potential confounding impact of hyperglycaemia on the level of GGT could not be investigated.

Compared with GGT, ALT is considered to be a better marker of non-alcoholic fatty liver disease (NAFLD), which is more prevalent in the obese. This may explain the differences between GGT and ALT in the prediction of diabetes according to BMI categories. A recent meta-analysis reported that ultrasonography-diagnosed NAFLD is associated with more than a doubling in the risk of incident diabetes [20]. However, in our study, the GGT level appeared to be a significant risk marker for incident diabetes independently of waist circumference or markers of liver function such as ALT. Furthermore, it has also been shown that increased serum GGT and ALT levels are independent risk factors for the development of type 2 diabetes mellitus in participants without fatty liver or hepatic dysfunction [21]. In non-diabetic men, GGT but not ALT levels were observed to be inversely related to insulin sensitivity independently of intra-abdominal fat area [22].

In contrast to that in the more obese participants, the association between GGT and incident diabetes in those with a BMI of <27 kg/m^2 was only slightly attenuated after adjustment for HOMA-IR or waist circumference, both of which are robust markers of insulin resistance and visceral fat. We speculate therefore that peripheral insulin resistance, which is less predominant in leaner participants than in markedly obese individuals, is not the main underlying mechanism explaining the relationship between GGT and type 2 diabetes in this group with a BMI of <27 kg/m^2. However, it should be noted that we did not assess insulin sensitivity by more accurate methods such as the euglycaemic–hyperinsulinaemic clamp or the Matsuda index [23].

The inclusion of a large number of individuals with normal body weight provided the opportunity to show the association between GGT levels and type 2 diabetes incidence without the confounding presence of excessive visceral or liver fat. The probability of substantial fatty liver among patients with a BMI of <27 kg/m^2 is low, suggesting alternative mechanisms to explain the association between GGT levels and the risk of diabetes in this population.

Moderately elevated GGT or ALT levels may be related to a reduced acute insulin response to glucose and/or a higher glycaemia peak in response to meals, explaining the association between GGT or ALT activities and the increased risk of type 2 diabetes. In this regard, it has been shown in Pima Indians that GGT and ALT levels were inversely correlated with peripheral and hepatic insulin sensitivity as

evaluated by the euglycaemic–hyperinsulinaemic clamp [24]. It has also been demonstrated that non-diabetic patients with impaired insulin secretion due to variants of the *TCF7L2* gene have an enhanced rate of hepatic glucose production [25], emphasising the tight link between beta cells and liver metabolism. We speculate that even moderately impaired insulin secretion may favour an increase in GGT or ALT levels through enhanced hepatic gluconeogenesis. A subtle elevation of GGT levels could therefore be viewed as an indirect marker of elevated hepatic insulin resistance and/or impaired insulin secretion [26]. In this regard, we found that plasma GGT was significantly correlated with the HOMA beta index [26] in our cohort (data not shown). Impaired early and total insulin secretion are viewed as strong determinants of future glucose tolerance in non-obese individuals and as the predominant features of newly diagnosed type 2 diabetes [27, 28].

Another mechanism involved in the association between GGT and the development of type 2 diabetes may be related to oxidative stress and the role of cellular GGT in the metabolism of extra-cellular reduced glutathione. Recent data suggest that cellular GGT may be involved in the production of reactive oxygen species in the presence of iron or other transition metals [29]. It has therefore been proposed that serum GGT might be an early and sensitive enzyme related to oxidative stress, which appears to play a role in the development of beta cell dysfunction and insulin resistance [30, 31].

Limitations of the present study include the absence of gold standard measures of insulin sensitivity and insulin secretion such as the euglycaemic–hyperinsulinaemic clamp or the insulinogenic index. In addition, we cannot formally prove the absence of substantial fatty liver in the participants with BMI of <27 kg/m^2 as no ultrasonography was performed. We also cannot rule out the possibility that the association between GGT and incident diabetes may be related, at least in part, to the adverse impact of chronic alcohol intake on the pancreas. Alcohol consumption may be a confounding factor, which is difficult to evaluate with possible underreporting and misclassification. However, the results were not altered after adjusting for alcohol consumption or exclusion of heavy drinkers. The strengths of the present study are the large population in the DESIR cohort, with a low rate of obesity and the study's prospective design with long follow-up.

In conclusion, the novel finding of our study is that an increase in GGT concentration within its physiological range is a sensitive and early biomarker for the development of type 2 diabetes among persons with a BMI of <27 or even <25 kg/m^2. This significant association between GGT and the risk of type 2 diabetes was independent of traditional risk factors for diabetes such as waist circumference and HOMA-IR, suggesting this variable could help better identify patients at risk of diabetes. Our findings also highlight early interactions between beta cells and the liver, which warrant further study.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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