4. Villanueva J, Shaffer DR, Philip J, Chaparro CA, Erdjument-Bromage H, Olshen AB, et al. Differential exoprotease activities confer tumor-specific serum peptidome patterns. J Clin Invest 2006;116:271–84.

5. Jin M, Cataland S, Bissell M, Wu HM. A rapid test for the diagnosis of thrombotic thrombocytopenic purpura using surface enhanced laser desorption/ionization time-of-flight (SELDI-TOF)-mass spectrometry. J Thromb Haemost 2006;4:333–8.

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Relationship between γ-Glutamyltransferase, Fasting Plasma Glucose, and Triglycerides in the General Population

To the Editor:

Recent population-based epidemiologic studies have convincingly shown that serum γ-glutamyltransferase (GGT) activity is associated with many cardiovascular disease risk factors and predicts new-onset type 2 diabetes, hypertension, stroke, and myocardial infarction *(1, 2)*. We read with interest the recent article by Lim et al. *(3)* on the possible interaction between GGT and obesity and its association with the risk of prevalent type 2 diabetes, findings indicating that obesity itself may not be a sufficient risk factor for diabetes when GGT concentrations approach the lower limit of the reference interval. The clinical implications of this conclusion are noteworthy because overweight-obese people with GGT concentrations at the lower limit of the reference interval (e.g., <20 U/L) would no longer be considered at high risk of developing diabetes. To further investigate the relationships among GGT, diabetes, and other major biochemical components of the metabolic syndrome in the general population, we analyzed whether serum GGT concentrations predict prevalent diabetes and hypertriglyceridemia, and whether there is an interaction between GGT and hypertriglyceridemia that affects the risk of prevalent diabetes.

We performed a retrospective analysis on the database of the laboratory information system of the clinical chemistry laboratory at the Verona University Hospital to retrieve test results for serum GGT, fasting plasma glucose (FPG), and triglyceride, which had been performed on the whole cohort of outpatients consecutively referred by general practitioners for routine blood testing in the preceding 9 months (August 2006–April 2007). Venous blood from outpatients was routinely collected in the morning from fasting individuals, and FPG, triglycerides, and GGT were assayed by enzymatic procedures on a Roche/Hitachi Modular System (Roche Diagnostics GmbH). We assessed the significance of differences and frequency distributions of values with the Kruskal–Wallis test and the χ^2 test (for categorical variables), respectively. Multivariable logistic regression analysis was used to examine the interaction relationship with diabetes, as the dependent variable, predicted from triglycerides (subdivided in tertiles: <0.95, 0.95–1.47, and >1.47 mmol/L) within 3 categories of GGT (<20, 20–39.9, and ≥40 U/L). Adjusting variables were age and sex. Statistical analyses were performed using the statistical package SPSS-version 12.

Cumulative results for GGT, FPG, and triglycerides were retrieved for 7267 outpatients >35 years old during a 9-month period. As shown in Table 1, the concentrations of FPG and triglycerides markedly increased among the GGT categories. Similarly, the frequency of those with FPG ≥7.0 mmol/L, a cutpoint suggestive for diagnosing diabetes according to the American Diabetes Association guidelines *(4)*, and of those with hypertriglyceridemia (≥1.7 mmol/L by the Third Adult Treatment Panel criteria) increased steadily across the spectrum of GGT thresholds from 16% to 31% for FPG and from 14% to 39% for triglycerides, respectively. These results remained unchanged after we adjusted for sex and age. Interestingly, as also shown in Table 1, the age-, and sex-adjusted frequencies of diabetes significantly increased across the tertiles of triglycerides within all 3 GGT categories, thus excluding the existence of a significant interaction between GGT and triglycerides on the risk for prevalent diabetes.

Increased concentrations of GGT, an enzyme associated with liver damage *(2)*, are conventionally interpreted as a marker of alcohol consumption. However, as previously reported, alcohol consumption could not entirely explain the association between increased GGT concentrations and type 2 diabetes, because this association was observed even after adjustment for daily alcohol intake and existed among nondrinkers *(1, 2)*. Moreover, it has been shown that increased GGT concentrations are associated with lipid abnormalities independently of obesity *(5)*. In the present study, we failed to find a significant interaction between GGT and triglycerides in predicting prevalent diabetes, suggesting that the association between triglycerides and diabetes might be only marginally influenced by serum GGT concentrations. Obviously, we must be cautious in making any causal inference because of the cross-sectional nature of our study, but such findings would not be unexpected because of the intertwined and complex biological relationships linking diabetes and hypertriglyceridemia. Nevertheless, our results do not exclude the possibility that increased GGT, as a marker of fatty liver, plays an important role in the development of type 2 diabetes *(1, 2)*.

Overall, we agree with the suggestions of Lim et al. *(3)* that GGT

Table 1. Baseline characteristics of the study participants (n = 7267) according to categories of serum GGT activity, and prevalence of diabetes (defined as those with FPG ≥7.0 mmol/L) by tertiles of plasma triglycerides after stratification by GGT categories.

	GGT categories (U/L)				
	<20	20–39.9	≥40	Unadjusted *P* values for trend	*P* values for trend adjusted for age and sex
n	3263	2468	1536		
Sex (% male)	57%	66%	78%	<0.0001	
Age (years)	54 (18)	60 (15)	60 (13)	<0.0001	
FPG, mmol/L					
Mean (SD)	5.9 (2.0)	6.4 (2.3)	6.8 (2.6)	<0.0001	<0.0001
%FPG ≥7.0	16%	24%	31%	<0.0001	<0.0001
Triglycerides, mmol/L					
Mean (SD)	1.2 (0.6)	1.5 (0.9)	1.8 (1.4)	<0.0001	<0.0001
%Triglycerides ≥1.7	14%	28%	39%	<0.0001	<0.0001

		Triglycerides tertiles (mmol/L)			
		<0.95	0.95–1.47	>1.47	*P* values for trend adjusted for age and sex
n		2399	2522	2346	
GGT categories (U/L)					
<20	%FPG ≥7, mmol/L	12.5%	15.3%	25.3%	<0.0001
20–39.9	%FPG ≥7, mmol/L	18.5%	23.2%	29.8%	<0.0001
≥40	%FPG ≥7, mmol/L	24.8%	27.3%	36.6%	<0.0001

measurement may be useful in clinical settings for detecting high-risk subpopulations of type 2 diabetes and/or hypertriglyceridemia. Such individuals might benefit from a more intensive therapeutic approach to decrease their global cardiovascular risk, regardless of potential unmeasured effects of lifestyle or obesity. Conceivably, the significant association of serum GGT concentrations with FPG and triglycerides, observed in our investigation, may be biologically explained by some underlying mechanisms such as hepatic steatosis, insulin resistance, and increased oxidative stress.

References

1. Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care 1998;21:732–7.
2. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, et al. Gamma-glutamyltransferase and diabetes: a 4 year follow-up study. Diabetologia 2003;46:359–64.
3. Lim JS, Lee DH, Park JY, Jin SH, Jacobs Jr DR. A strong interaction between serum gamma-glutamyltransferase and obesity on the risk of prevalent type 2 diabetes: results from the Third National Health and Nutrition Examination Survey. Clin Chem 2007;53:1092–8.
4. American Diabetes Association. Standard of medical cares in diabetes. Diabetes Care 2007;30(Suppl 1):S4–41.
5. Lim JS, Kim YJ, Chun BY, Yang JH, Lee DH, Kam S. The association between serum GGT level within normal range and risk factors of cardiovascular diseases. J Prev Med Pub Health 2005;38:101–6.

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Effect of Serum Gamma-Glutamyltransferase and Obesity on the Risk of Dyslipidemia and Poor Glycemic Control in Type 2 Diabetic Patients: Cross-Sectional Findings from the Verona Diabetes Study

To the Editor:

We read with interest the article by Lim et al. *(1)* regarding a strong interaction between serum gamma-glutamyltransferase (GGT) activity and body mass index (BMI) and their effect on the risk of prevalent diabetes. The authors found that BMI is associated with prevalent diabetes only among individuals with high-normal GGT, suggesting that GGT determination can be useful in clinical settings for identifying individuals at high risk for diabetes.

Given the scientific and clinical importance of an interaction between obesity and GGT in predicting diabetes, we investigated possible interactions between BMI and GGT in predicting poor glycemic control and common comorbidities of diabetes. Therefore, we assessed whether the association of BMI with hypertension, dyslipidemia, and poor glyce-