Serum γ-glutamyltransferase (GGT) concentration within its normal range has emerged as an important predictor in the pathogenesis of diabetes. We studied serum GGT as a predictor of type 2 diabetes incidence and a possible interaction between obesity and GGT on the development of type 2 diabetes in men and women. A prospective cohort study of 20,158 Finnish men and women aged 25–64 yr who participated in cardiovascular risk-factor surveys carried out in four areas during 10 yr. The average follow-up time was 12.7 yr, and there were 388 incident diabetes cases. Serum GGT cut points were at the 25th, 50th, 75th, and 90th percentiles. Initiation of new diabetes medication defined incidence cases. After adjustment for known risk factors of type 2 diabetes, relative risks for incident diabetes across GGT categories were 1.0, 1.2, 2.3, 3.1, and 3.9 among men and 1.0, 0.8, 1.7, 3.5, and 6.4 among women (P for trend < 0.01, respectively). Body mass index appeared to be more strongly associated with type 2 diabetes in both men and women over age 50 yr with GGT median or greater, compared with subjects with GGT less than median.

In conclusion, in women as well as men, serum GGT level modified the well-known association between body mass index and type 2 diabetes. (J Clin Endocrinol Metab 89: 5410–5414, 2004)

Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein.

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diabetes at baseline identified by the national diabetes registry, which includes subjects receiving reimbursement for their diabetes medication, before the survey and by a survey question about diabetes diagnosed by a physician. Another 43 participants were excluded because of missing data on GGT. A total of 9,771 men and 10,387 women were included in the present analyses. They were followed up through the end of 1997 or until death or the diagnosis of diabetes.

Alcohol drinking, smoking status, and physical activity at baseline were assessed with a set of standardized questions in a self-administered questionnaire mailed to the participants in advance. Alcohol drinking was assessed on the basis of the self-reported number of drinks consumed during the previous week. Physical activity was measured by asking whether the participant practiced leisure time physical activity at least 20–30 min two times or more per week.

At the survey site, specially trained research nurses measured height, weight, and blood pressure by using the standardized methods for the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease protocol (13). Systolic and diastolic blood pressures were measured twice, and the mean of these measurements was used in the analyses. BMI (kilograms per square meter) was used as a measure of relative body weight. A venous blood specimen was taken for biochemical measurements; fasting was not required for all surveys. GGT and insulin levels, which were available for a subset only. In addition, for a subsample of men and women, fasting glucose (n = 4661) and insulin levels (n = 1617) were determined from frozen plasma. All samples were analyzed in the same central laboratory at the Finnish National Public Health Institute.

Data on the occurrence of new diabetes cases during the follow-up were obtained from the National Social Insurance Institution’s register. Thus, the data include diabetes treated by drugs but not diet only. Women with gestational diabetes, who need a short-term drug treatment, are not included in the register. We excluded type 1 diabetes cases by checking the National Hospital Discharge register that provides separate diagnosis codes for types 1 and 2 diabetes. The number of new type 2 diabetes cases during the follow-up was 212 among men and 176 among women.

All analyses were separately performed in men and women. Serum GGT levels were classified into five groups using the 25th, 50th, 75th, and 90th percentiles as cut points. The cut points were 15, 21, 33, and 57 U/liter among men (normal range = 5–50 U/liter) and 9, 12, 17, and 28 U/liter among women (normal range = 40 U/liter). For calculation of incidence density, length of follow-up was calculated as days from the baseline exam to diabetes diagnosis. Cox proportional hazard models were used to calculate multivariate-adjusted hazard ratios, using the PHREG procedure of the SAS statistical package (14). Deaths were censored at the time of death based on the Mortality Register of Statistics Finland. Covariates were the baseline values of age, BMI, alcohol consumption, cigarette smoking, and physical activity as well as plasma glucose and insulin levels, which were available for a subset only. In addition, we assessed whether the associations among age, BMI, and type 2 diabetes were modified by baseline serum GGT level. The median value of serum GGT level was used as the cut-off point in interaction or stratified analyses.

**Results**

At baseline, serum GGT was related to most cardiovascular risk factors in both men and women (Table 1). Alcohol consumption, age, cigarette smoking, and BMI were positively associated with baseline serum GGT level. Among clinical variables, systolic and diastolic blood pressure, fast-

**TABLE 1.** Age-adjusted risk factor levels at baseline in 1982, 1987, or 1992 in men and women aged 25–64 yr, by serum GGT level

<table>
<thead>
<tr>
<th>Men</th>
<th>Baseline GGT level</th>
<th>&lt;25%</th>
<th>25–50%</th>
<th>50–75%</th>
<th>75–90%</th>
<th>≥90%</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2381</td>
<td>2391</td>
<td>2558</td>
<td>1454</td>
<td>997</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42.4</td>
<td>44.0</td>
<td>45.3</td>
<td>45.5</td>
<td>46.2</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/wk)</td>
<td>37.9</td>
<td>39.7</td>
<td>41.5</td>
<td>43.4</td>
<td>45.0</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>32.9</td>
<td>37.9</td>
<td>42.4</td>
<td>45.8</td>
<td>48.5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td>45.3</td>
<td>43.1</td>
<td>40.4</td>
<td>36.5</td>
<td>36.0</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8</td>
<td>25.7</td>
<td>27.1</td>
<td>27.8</td>
<td>28.5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>239.1</td>
<td>140.4</td>
<td>142.1</td>
<td>144.0</td>
<td>147.3</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>82.8</td>
<td>83.8</td>
<td>86.3</td>
<td>88.4</td>
<td>91.4</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/liter)</td>
<td>4.44</td>
<td>4.45</td>
<td>4.77</td>
<td>4.87</td>
<td>5.34</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Fasting serum insulin (µU/liter)</td>
<td>5.38</td>
<td>6.80</td>
<td>7.85</td>
<td>9.52</td>
<td>10.61</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/liter)</td>
<td>5.73</td>
<td>5.93</td>
<td>6.10</td>
<td>6.26</td>
<td>6.37</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Serum HDL-C (mmol/liter)</td>
<td>1.29</td>
<td>1.28</td>
<td>1.23</td>
<td>1.22</td>
<td>1.28</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women (n = 10387)</th>
<th>Baseline GGT level</th>
<th>&lt;8 U/liter</th>
<th>9–11 U/liter</th>
<th>12–16 U/liter</th>
<th>17–27 U/liter</th>
<th>≥28 U/liter</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2080</td>
<td>2842</td>
<td>2703</td>
<td>1747</td>
<td>1015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40.7</td>
<td>43.3</td>
<td>45.4</td>
<td>47.5</td>
<td>49.4</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/wk)</td>
<td>10.1</td>
<td>14.6</td>
<td>22.8</td>
<td>26.2</td>
<td>32.4</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>14.0</td>
<td>18.8</td>
<td>23.9</td>
<td>27.8</td>
<td>31.1</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td>39.9</td>
<td>41.3</td>
<td>39.7</td>
<td>40.8</td>
<td>38.0</td>
<td>0.414</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9</td>
<td>25.0</td>
<td>25.8</td>
<td>27.0</td>
<td>27.8</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>134.1</td>
<td>134.8</td>
<td>136.5</td>
<td>138.6</td>
<td>139.6</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81.6</td>
<td>80.1</td>
<td>81.6</td>
<td>82.9</td>
<td>84.1</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/liter)</td>
<td>4.40</td>
<td>4.53</td>
<td>4.59</td>
<td>4.77</td>
<td>4.91</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Fasting serum insulin (µU/liter)</td>
<td>5.37</td>
<td>6.19</td>
<td>6.91</td>
<td>8.42</td>
<td>9.71</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/liter)</td>
<td>5.81</td>
<td>5.86</td>
<td>5.87</td>
<td>5.91</td>
<td>5.94</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Serum HDL-C (mmol/liter)</td>
<td>1.53</td>
<td>1.54</td>
<td>1.52</td>
<td>1.48</td>
<td>1.48</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Leisure time physical activity two times per week or more.

^a Fasting plasma glucose was measured among 2205 men and 2456 women.

^b Fasting serum insulin was measured among 744 men and 873 women.
ing plasma glucose, fasting insulin, and total cholesterol also showed positive associations with baseline GGT level, whereas HDL-cholesterol showed a U-shaped association in men but an inverse association in women.

Compared with the lowest baseline GGT category, the relative risks of incident type 2 diabetes adjusted for age were 1.5, 3.5, 5.7, and 6.7 (test P for trend < 0.01) among men and 1.0, 2.0, 4.7, and 9.0 (test P for trend < 0.01) among women in the other four GGT categories (Table 2). Additional adjustment for BMI, alcohol consumption, cigarette smoking, and physical activity attenuated this relationship, but GGT still remained a strong risk factor for type 2 diabetes among both genders; adjusted relative risks were 1.0, 1.2, 2.3, 3.1, and 3.9 (test P for trend < 0.01) among men and 1.0, 8.0, 17.3, 5.7, and 6.4 (test P for trend < 0.01) among women in the five GGT categories, respectively. Further adjustment for baseline fasting serum glucose did not materially alter the association with GGT. The positive association between baseline GGT and incident type 2 diabetes was observed in both alcohol drinkers and nondrinkers. For example, after adjusting for age, BMI, cigarette smoking, and physical activity, relative risks among nondrinkers were 1.00, 0.87, 1.89, 2.32, and 2.37 (test P for trend < 0.01) among men and 1.00, 0.77, 1.85, 3.65, and 5.67 (test P for trend < 0.01) among women.

The association of BMI with incident type 2 diabetes appeared to be modified by GGT. Compared with men with GGT below the median, among men with GGT above the median, BMI was more strongly associated with incident type 2 diabetes (P for interaction = 0.10) (Fig. 1). In women, the interaction appeared to be restricted to women aged 50 yr or older (P for the interaction = 0.24) (Fig. 2). We stratified women by age 50 yr as a surrogate of menopausal status. On the other hand, the association of age with incident type 2 diabetes was not different, depending on baseline GGT level (data not shown).

**Discussion**

In the present study, higher serum GGT concentration was directly associated with the increased risk of type 2 diabetes in both genders. The association was strong, graded, and not confounded by BMI and lifestyle factors. Our data are in agreement with results of previous prospective studies in men (4, 8) or pooling findings for men and women (9), which showed that baseline serum GGT level within its normal range was an independent risk factor for the development of diabetes. These studies cover several ethnic groups, including British men selected from lists of general practitioners (4), Korean steelworkers (8), a population-based sample of black and white American men and women (9), and, in the current study, a population-based sample of middle-aged Finnish men and women. In contrast, a study (15) in Pima Indians reported no association of GGT level with incident diabetes; this study is discussed below.

Elevated GGT is conventionally interpreted as a marker of alcohol abuse (10). However, in the previous studies (4, 8, 9), in both genders. The association was strong, graded, and not confounded by BMI and lifestyle factors. Our data are in agreement with results of previous prospective studies in men (4, 8) or pooling findings for men and women (9), which showed that baseline serum GGT level within its normal range was an independent risk factor for the development of diabetes. These studies cover several ethnic groups, including British men selected from lists of general practitioners (4), Korean steelworkers (8), a population-based sample of black and white American men and women (9), and, in the current study, a population-based sample of middle-aged Finnish men and women. In contrast, a study (15) in Pima Indians reported no association of GGT level with incident diabetes; this study is discussed below.

![Fig. 1. Interaction between baseline BMI and serum GGT on the risk of incident type 2 diabetes among men. Adjusted for baseline age, alcohol consumption, cigarette smoking, and physical activity.](image-url)

**TABLE 2.** Hazard ratios of type 2 diabetes associated with serum GGT levels in men and women aged 25–64 yr, adjusting for baseline factors

<table>
<thead>
<tr>
<th>Baseline serum GGT level</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25% 14 U/liter</td>
<td>26</td>
<td>91</td>
</tr>
<tr>
<td>25–50% 15–20 U/liter</td>
<td>67</td>
<td>34</td>
</tr>
<tr>
<td>50–75% 21–32 U/liter</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>75–90% 33–56 U/liter</td>
<td>44</td>
<td>61</td>
</tr>
<tr>
<td>≥90%  ≥57 U/liter</td>
<td>44</td>
<td>61</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P of trend</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.01</td>
<td>44</td>
<td>61</td>
</tr>
</tbody>
</table>

**Table 2.** Hazard ratios of type 2 diabetes associated with serum GGT levels in men and women aged 25–64 yr, adjusting for baseline factors

<table>
<thead>
<tr>
<th>Model</th>
<th>Adjusted relative risk</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.0 (0.8–2.7)</td>
<td>3.5 (2.1–5.9)</td>
<td>5.7 (3.4–9.8)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0 (1.2–4.0)</td>
<td>2.3 (1.4–4.0)</td>
<td>3.1 (1.8–5.4)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.0 (0.3–1.8)</td>
<td>1.7 (0.8–3.5)</td>
<td>3.5 (1.8–7.0)</td>
</tr>
</tbody>
</table>

Model 1, Adjustment for age.
Model 2, Model 1 plus adjustment for baseline BMI, cigarette smoking, alcohol consumption, and physical activity.
Model 3, Model 2 plus adjustment for baseline fasting plasma glucose (measured among 2205 men and 2456 women). Thus, this model was restricted to these 4661 subjects.
alcohol consumption could not explain the association be-
tween GGT and incident diabetes. Again, in our study, the
association of GGT with incident type 2 diabetes was inde-
pended of alcohol intake and existed among nondrinkers as
well. Recently because fatty liver has been linked to the
insulin resistance syndrome and/or type 2 diabetes (16, 17),
GGT might be interpreted as a marker for hepatic steatosis
and hepatic insulin resistance in the pathogenesis of type 2
diabetes (4). The present data had no information on more
liver-specific enzymes such as alanine aminotransferase
(ALT) or aspartate aminotransferase (AST). However, our
previous two studies (8, 9) showed that the dose-response
relationship between GGT level and incidence of diabetes
was also observed among subjects within the normal range
of ALT or AST. In addition, the associations between ALT or
AST and diabetes were weaker than those of GGT and were
mostly restricted to abnormal levels of liver enzymes (4, 8, 9).

However, one prospective study (15) in Pima Indians has
reported that higher ALT, but not GGT, predicted type 2
diabetes. Their baseline mean values of ALT, AST, and GGT
were above the upper limit of normal range: about 2 times
higher than those of the previous studies (4, 8, 9) in which
GGT was more strongly associated with diabetes. Because
clinical studies (18, 19) have consistently reported an asso-
ciation between several pathologic liver conditions and type
2 diabetes, the results in Pima Indians might reflect the asso-
ciation between liver damage and type 2 diabetes.

Although the mechanisms underlying the above associa-
tion remain largely unknown, certain mechanisms related to
oxidative stress might play a role. There is clear evidence that
cellular GGT level is closely related to oxidative stress indica-
tors in vivo, either as an antioxidant or a prooxidant, de-
pending on circumstances (20–26). Although the relation
between cellular and serum GGT is unclear, supporting a
role of cellular GGT in the oxidative stress, our previous
studies (9, 27–29) in Coronary Artery Risk Development in
Young Adults (CARDIA) subjects have consistently shown
that serum GGT within its normal range might be related to
oxidative stress.

Consistent with our previous findings (8, 9), we observed
that BMI was a stronger risk factor for incident type 2 dia-
betes among subjects with high normal GGT than in those
with low normal GGT. Even though the interaction was
observed among both genders, in women it was mostly
shown among women aged 50 yr or older; most of whom
were probably postmenopausal. A possible interpretation
of this interaction between BMI and GGT is that obese subjects
with high normal GGT have already suffered subclinical
pathological changes due to obesity, whereas obese subjects
with low normal GGT are at an earlier stage of pathogenesis.
According to this interpretation, serum GGT level might be
an intervening factor in the association between obesity and
diabetes. If this is true, an adjustment for GGT should have
attenuated the association between BMI and type 2 diabetes.
However, the adjustment for GGT did not materially change
the association between BMI and the incidence of type 2
diabetes.

In our previous study of Korean men (8), age was a strong
risk factor for diabetes only among subjects with high normal
GGT; however, both CARDIA (9) and Finnish data failed to
show an interaction between GGT and age. In our previous
paper (9), we interpreted that a young age distribution in the
CARDIA cohort might explain the different result between
Korean and CARDIA data because the interaction with age
in the Korean study was largely restricted to participants
who were 45 yr old or more. However, the present data did
not show the interaction between age and GGT, despite
similarity of age distribution with Korean data, suggesting
that our previous finding might have been due to chance. On
the other hand, racial difference or leanness of Korean men
might explain the different result.

Our study has several limitations. First, there was a pos-
sibility of underdiagnosis of incident type 2 diabetes because
only drug-treated diabetes was regarded as the outcome.
However, the underdiagnosis might attenuate the strength of
association because there is a clear positive association be-
tween serum GGT and fasting serum glucose. Second, even
though we interpreted that our finding might not relate to
liver disease, that judgment was made based on our previous
studies (8, 9), not the present results.
In conclusion, this study suggests that serum GGT is a strong and independent predictor of type 2 diabetes in both genders, irrespective of alcohol consumption. We speculate that it might be involved in the pathogenesis in diabetes through a mechanism related to oxidative stress. In addition, the well-known associations of BMI with diabetes may be modified by serum GGT level. For the prediction of type 2 diabetes in obese subjects, it may be useful to determine serum GGT because it is easy and inexpensive to measure and strongly modifies the obesity related type 2 diabetes risk.

Acknowledgments

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References


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