Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes

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OBJECTIVE—To investigate the association of normal fasting plasma glucose (FPG) and the risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS—Data concerning 13,845 subjects, aged 40–69 years, who had their FPG measured at least three times between 1992 and 2008 were extracted from a database. Three FPG groups were defined (51–82, 83–90, and 91–99 mg/dL). A Cox proportional hazards analysis was applied to estimate the risk of incident diabetes adjusted for other risk factors.

RESULTS—During 108,061 person-years of follow-up (8,110 women and 5,735 men), 307 incident cases of type 2 diabetes were found. The final model demonstrated a hazard ratio of 2.03 (95% CI 1.18–3.50) for 91–99 mg/dL and 1.42 (0.42–4.74) for 83–90 mg/dL.

CONCLUSIONS—Our data suggest that FPG between 91 and 99 mg/dL is a strong independent predictor of type 2 diabetes and should be used to identify people to be further investigated and aided with preventive measures.

The prevalence of type 2 diabetes is increasing worldwide (1,2). Prediction methods are a matter of discussion (3–5). A recent study (6) showed an alteration of normal linear trajectories for fasting and postload plasma glucose concentrations and insulin sensitivity and secretion 3–6 years before diagnosis. Other studies (7,8) showed an increased risk of developing type 2 diabetes among normoglycemic subjects, particularly in those with a fasting plasma glucose (FPG) range of 91–99 mg/dL. Clear information regarding Mediterranean populations is lacking. We investigated whether the higher tertiles of within-normal-range FPG concentrations in a northern Italian population can help identify people at increased risk.

RESEARCH DESIGN AND METHODS—The Italian National Health Service facilitates health controls; on average, northern Italian individuals have one annual blood drawing with eight laboratory tests, including FPG. This induced us to use retrospective outpatient data of the Desio Hospital Laboratory to model an experimental population.

Selection criteria were basal FPG <100 mg/dL at inclusion; at least three additional FPG measurements between 1992 and 2008; and total, HDL, and LDL cholesterol and triglyceride measurements. Furthermore, they did not have any requests for glycated hemoglobin, a limit set to avoid inclusion of those with type 1 and type 2 diabetes.

A total of 13,845 people, aged 40–69 years (9), were considered. These subjects represented 17% of the corresponding stratum (82,000), which is 41% (equivalent to Milan province census data) of the general population (200,000) referring to our laboratory. Demographic and health status information collected through a questionnaire (from 1992 to 2008) was available for a random (one of four consecutive) subset of 3,593 outpatients. We diagnosed type 2 diabetes (study end point) after two FPG concentrations >125 mg/dL (10,11).

Blood samples, collected in lithium-heparin tubes, were analyzed by the enzymatic and colorimetric method (GOD-PAP) within 2 h. Analytical variability was within 2% (12). Data were stratified in groups according to three FPG concentration ranges (51–82, 83–90, and 91–99 mg/dL). Baseline characteristics (mean age, follow-up time, and lipids) across FPG groups were investigated.

The Cochrane-Armitage trend test was used to fit the median of each biomarker in the FPG group to estimate two-sided P values for trends of biomarkers across groups of FPG. A Cox proportional hazards analysis to estimate the hazard ratios and 95% CIs for the development of type 2 diabetes was applied; the values for age, then for triglycerides and total, HDL, and LDL cholesterol were subsequently added. The final Cox model applied to the subset group with health status information was adjusted for sex, age, triglycerides, total cholesterol, BMI, hypertension, family history of type 2 diabetes, smoking, and drinking habits. Statistical analyses were performed (SAS version 8.3; SAS Institute, Inc., Cary, NC).

RESULTS—Data from 8,110 women and 5,735 men with mean (±SD) ages at baseline of 53.8 ± 8.18 and 54.1 ± 8.24 years were observed for an average of 7.9 and 7.4 years (range 1–16 years), respectively. Triglycerides and LDL and total cholesterol increased across FPG groups in both sexes, whereas HDL cholesterol decreased only in women (Table 1).

The longitudinal assessment of blood glucose levels and progression to diabetes is reported in Supplementary Table A1 and Supplementary Fig. A1.

During 108,061 person-years of follow-up, there were 307 incident cases of type 2 diabetes. Incidence was 1.9% for women and 2.7% for men. The incidence of type 2 diabetes increased across FPG groups from 0.73 and 0.58% in the 51–82
Table 1—Baseline characteristics, incident cases, and hazard ratios for type 2 diabetes for 8,110 women and 5,735 men, aged 40–69 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
<th>P for trend*</th>
<th>Women</th>
<th>Men</th>
<th>P for trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51–82 mg/dL</td>
<td>83–90 mg/dL</td>
<td>91–99 mg/dL</td>
<td>51–82 mg/dL</td>
<td>83–90 mg/dL</td>
<td>91–99 mg/dL</td>
</tr>
<tr>
<td>n</td>
<td>2,254</td>
<td>3,009</td>
<td>2,847</td>
<td>1,039</td>
<td>1,902</td>
<td>2,794</td>
</tr>
<tr>
<td>Age</td>
<td>54.4 ± 8.5</td>
<td>55.5 ± 8.5</td>
<td>56.4 ± 8.3</td>
<td>&lt;0.001</td>
<td>54.8 ± 8.8</td>
<td>56.2 ± 8.8</td>
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<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
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<tr>
<td>Means ± SD</td>
<td>77.2 ± 4.6</td>
<td>86.6 ± 2.2</td>
<td>94.6 ± 2.6</td>
<td>&lt;0.001</td>
<td>77.5 ± 4.3</td>
<td>86.8 ± 2.2</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>78 (75–81)</td>
<td>87 (85–89)</td>
<td>95 (92–97)</td>
<td>&lt;0.001</td>
<td>79 (75–81)</td>
<td>87 (85–89)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Means ± SD</td>
<td>98.7 ± 47.5</td>
<td>105.2 ± 51.9</td>
<td>113.3 ± 58.0</td>
<td>&lt;0.001</td>
<td>132.1 ± 74.3</td>
<td>132.3 ± 70.6</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>87 (67–117)</td>
<td>92 (70–127)</td>
<td>100 (73–137)</td>
<td>&lt;0.001</td>
<td>112 (84–160)</td>
<td>116 (83–160)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Means ± SD</td>
<td>210.4 ± 39.2</td>
<td>184.5 ± 32.8</td>
<td>218.6 ± 38.9</td>
<td>&lt;0.001</td>
<td>204.2 ± 38.7</td>
<td>207.3 ± 37.7</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>208 (183–234)</td>
<td>182 (163–202)</td>
<td>216 (192–243)</td>
<td>&lt;0.001</td>
<td>203 (178–228)</td>
<td>206 (182–231)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Means ± SD</td>
<td>63.3 ± 15.8</td>
<td>62.8 ± 16.2</td>
<td>61.4 ± 16.0</td>
<td>&lt;0.001</td>
<td>51.1 ± 14.3</td>
<td>51.6 ± 14.1</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>62 (53–72)</td>
<td>62 (52–72)</td>
<td>60 (50–71)</td>
<td>&lt;0.001</td>
<td>49 (42–58)</td>
<td>49 (42–58)</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
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<td></td>
<td></td>
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<tr>
<td>Means ± SD</td>
<td>130.6 ± 37.6</td>
<td>135.9 ± 35.7</td>
<td>138.3 ± 36.8</td>
<td>&lt;0.001</td>
<td>131.1 ± 36.3</td>
<td>133.6 ± 35.1</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>129 (105–135)</td>
<td>134 (111–158)</td>
<td>136 (113–162)</td>
<td>&lt;0.001</td>
<td>131 (107–154)</td>
<td>133 (110–153)</td>
</tr>
<tr>
<td>Time of follow-up (year)</td>
<td>8.0</td>
<td>7.9</td>
<td>8.0</td>
<td>0.53</td>
<td>7.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Incident cases of diabetes (n)</td>
<td>17</td>
<td>41</td>
<td>96</td>
<td>&lt;0.001</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Incidence of diabetes (%)</td>
<td>0.75</td>
<td>1.36</td>
<td>3.37</td>
<td>0.58</td>
<td>1.74</td>
<td>4.08</td>
</tr>
<tr>
<td>Rate†</td>
<td>0.94</td>
<td>1.70</td>
<td>4.20</td>
<td>0.76</td>
<td>2.26</td>
<td>5.40</td>
</tr>
<tr>
<td>Hazard ratios (95% CI)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.00</td>
<td>2.10 (1.13–3.90)</td>
<td>2.89 (2.18–3.83)</td>
<td></td>
<td>1.00</td>
<td>2.59 (1.24–5.40)</td>
</tr>
<tr>
<td>Adjusted for age; triglycerides; and total, HDL, and LDL cholesterol</td>
<td>1.00</td>
<td>1.93 (1.03–3.59)</td>
<td>2.87 (2.16–3.82)</td>
<td></td>
<td>1.00</td>
<td>2.58 (1.24–5.37)</td>
</tr>
</tbody>
</table>

The final Cox model was not stratified by sex because there were no differences between sexes, but it was adjusted for age, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, BMI, hypertension, family history of type 2 diabetes, smoking, and drinking habits. The model showed a hazard ratio of 2.03 (95% CI 1.18–3.50) for the 91–99 mg/dL FPG category and 1.42 (0.42–4.74) for the 86–90 mg/dL category. *P for trend was estimated using the Cochrane-Armitage trend test. †Rate was calculated as the number of incident cases of type 2 diabetes per 1,000 person-years. ‡A Cox proportional hazards analysis was applied to determine hazard ratios.
mg/dL category to 3.37 and 4.08% in the 91–99 mg/dL category, respectively, for women and men. In these groups, both women and men developed type 2 diabetes at a rate of 4.2 and 5.4 cases per 1,000 person-years, respectively.

Hazard ratios for type 2 diabetes adjusted only for age increased across groups of normal FPG, reaching 2.89 (95% CI 2.18–3.83) for women and 2.87 (2.03–4.04) for men in the highest FPG group. Additional adjustment for lipids did not significantly change risk. Men and women in the 91–99 mg/dL category showed the same hazard ratio (Table 1). The final model (not sex stratified), adjusted for recorded health status information, showed a hazard ratio of 2.03 (1.18–3.50) for the 91–99 mg/dL FPG category and 1.42 (0.42–4.74) for the 86–90 mg/dL category (Table 1).

**CONCLUSIONS**—During the follow-up of 13,845 apparently healthy Mediterranean adults, we found an increased risk of type 2 diabetes across FPG groups within normal range (10,11), suggesting that FPG between 91 and 99 mg/dL is a strong independent predictor of diabetes. This is in agreement with changes in glucose concentrations, insulin sensitivity, and secretion 3–6 years before the diagnosis (6). The increased risk (2.03) in the highest FPG group confirms that of 2.33 observed by Nichols et al. (8). The results indicate that elevated normal FPG may help select people at higher risk for future type 2 diabetes without the addition of strong independent risk factors, such as age, cholesterol, and triglycerides. Model adjustment for hypertension, BMI, and family history attenuates the hazard ratio (from 2.8 to 2.03).

The FPG range of 91–99 mg/dL can therefore be used to select those individuals to be subjected to further investigation with biomarkers of β-cell function, such as 1-h oral glucose tolerance test (OGTT) (5,13). In fact, a threefold decline in insulin sensitivity was demonstrated with increasing FPG levels from 70 to 125 mg/dL (14). The relationship between abnormal FPG and abnormal OGTT to the development of type 2 diabetes still remains an open question because some individuals develop abnormal FPG without developing abnormal OGTT and vice versa (15).

The incidence of diabetes in our study (2.7%) is higher than that in Tirosh et al. (7) (1.6%), perhaps because of the older population (mean age 54.1 vs. 32 years), yet is almost half of that (4.7%) described by Nichols et al. (8), who used less stringent criteria for diagnosis (only one FPG measurement >125 mg/dL with respect to our two) (10).

In conclusion, these results may help physicians to better identify those individuals who need further investigation and preventive measures. They can therefore support public health policy with an inexpensive tool for improving care and reducing costs of future treatment.

Acknowledgments—No potential conflicts of interest relevant to this article were reported. P.B. conceived the plan of analysis, researched data, reviewed data analysis, and contributed to discussion. E.L.V. extracted information, showed a hazard ratio of 2.03 (1.18–3.50) for the 91–99 mg/dL FPG category and 1.42 (0.42–4.74) for the 86–90 mg/dL category (Table 1).