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.

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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 0.75 and 0.58% in the 51–82

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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*

	Women				Men			
Variable	51–82 mg/dL	83–90 mg/dL	91–99 mg/dL	*P* for trend*	51–82 mg/dL	83–90 mg/dL	91–99 mg/dL	*P* for trend*
n	2,254	3,009	2,847		1,039	1,902	2,794	
Age	54.4 ± 8.5	55.5 ± 8.5	56.4 ± 8.3	<0.001	54.8 ± 8.8	56.2 ± 8.8	55.7 ± 8.7	0.17
FPG (mg/dL)								
Mean ± SD	77.2 ± 4.6	86.6 ± 2.2	94.6 ± 2.6		77.5 ± 4.3	86.8 ± 2.2	95.0 ± 2.6	
Median (interquartile range)	78 (75–81)	87 (85–89)	95 (92–97)	<0.001	79 (75–81)	87 (85–89)	95 (93–97)	<0.001
Triglycerides (mg/dL)								
Mean ± SD	98.7 ± 47.5	105.2 ± 51.9	113.3 ± 58.0		132.1 ± 74.3	132.3 ± 70.6	138.1 ± 71.9	
Median (interquartile range)	87 (67–117)	92 (70–127)	100 (73–137)	<0.001	112 (84–160)	116 (83–160)	121 (87–169)	<0.001
Cholesterol (mg/dL)								
Mean ± SD	210.4 ± 39.2	184.5 ± 32.8	218.6 ± 38.9		204.2 ± 38.7	207.3 ± 37.7	210.9 ± 38.3	
Median (interquartile range)	208 (183–234)	182 (163–202)	216 (192–243)	<0.001	203 (178–228)	206 (182–231)	209 (184–235)	<0.001
HDL cholesterol (mg/dL)								
Mean ± SD	63.3 ± 15.8	62.8 ± 16.2	61.4 ± 16.0		51.1 ± 14.3	51.6 ± 14.1	50.8 ± 13.7	
Median (interquartile range)	62 (53–72)	62 (52–72)	60 (50–71)	<0.001	49 (42–58)	49 (42–60)	49 (41–59)	0.70
LDL cholesterol (mg/dL)								
Mean ± SD	130.6 ± 37.6	135.9 ± 35.7	138.3 ± 36.8		131.1 ± 36.3	133.6 ± 35.1	137.0 ± 35.4	
Median (interquartile range)	129 (105–154)	134 (111–158)	136 (113–162)	<0.001	131 (107–154)	133 (110–155)	136 (113–159)	0.002
Time of follow-up (year)	8.0	7.9	8.0	0.53	7.5	7.6	7.6	0.28
Incident cases of diabetes (*n*)	17	41	96	<0.001	6	33	114	<0.001
Incidence of diabetes (%)	0.75	1.36	3.37		0.58	1.74	4.08	
Rate†	0.94	1.70	4.20		0.76	2.26	5.40	
Hazard ratios (95% CI)‡								
Adjusted for age	1.00	2.10 (1.13–3.90)	2.89 (2.18–3.83)		1.00	2.59 (1.24–5.40)	2.87 (2.03–4.04)	
Adjusted for age, triglycerides, and total, HDL, and LDL cholesterol	1.00	1.93 (1.03–3.59)	2.87 (2.16–3.82)		1.00	2.58 (1.24–5.37)	2.78 (1.98–3.92)	

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.

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P.B. conceived the plan of analysis, researched data, reviewed data analysis, and contributed to discussion. E.L.V. extracted data, performed data analysis, contributed to discussion, and drafted the manuscript. R.F. contributed to the review and revision of the manuscript. G.L. researched data and contributed to data analysis. S.S. and F.C. contributed to data research. P.M. conceived the plan of analysis, reviewed data analysis, contributed to discussion, and revised and approved the manuscript.

References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
3. Wilson PWF, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med 2007;167:1068–1074
4. Abdul-Ghani MA, Williams K, DeFronzo RA, Stern M. What is the best predictor of future type 2 diabetes? Diabetes Care 2007;30:1544–1548
5. Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA, Groop L. Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. Diabetes Care 2009;32:281–286
6. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 2009;373:2215–2221
7. Tirosh A, Shai I, Tekes-Manova D, et al.; Israeli Diabetes Research Group. Normal fasting plasma glucose levels and type 2 diabetes in young men. N Engl J Med 2005;353:1454–1462
8. Nichols GA, Hillier TA, Brown JB. Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. Am J Med 2008;121:519–524
9. Bonora E, Kiechl S, Willeit J, et al.; Bruneck Study. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck Study. Diabetes 2004;53:1782–1789
10. Genuth S, Alberti KG, Bennett P, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167
11. American Diabetes Association. Standards of medical care in diabetes: 2007. Diabetes Care 2007;30(Suppl. 1):S4–S41
12. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436–472
13. Abdul-Ghani MA, DeFronzo RA. Plasma glucose concentration and prediction of future risk of type 2 diabetes. Diabetes Care 2009;32(Suppl. 2):S194–S198
14. Dagogo-Jack S, Askari H, Tykodi G. Glucoregulatory physiology in subjects with low-normal, high-normal, or impaired fasting glucose. J Clin Endocrinol Metab 2009;94:2031–2036
15. Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R; Baltimore Longitudinal Study of Aging. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes 2003;52:1475–1484