ORIGINAL ARTICLE

Normal Fasting Plasma Glucose Levels and Type 2 Diabetes in Young Men

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ABSTRACT

BACKGROUND

The normal fasting plasma glucose level was recently defined as less than 100 mg per deciliter (5.55 mmol per liter). Whether higher fasting plasma glucose levels within this range independently predict type 2 diabetes in young adults is unclear.

METHODS

We obtained blood measurements, data from physical examinations, and medical and lifestyle information from men in the Israel Defense Forces who were 26 to 45 years of age.

RESULTS

A total of 208 incident cases of type 2 diabetes occurred during 74,309 person-years of follow-up (from 1992 through 2004) among 13,163 subjects who had baseline fasting plasma glucose levels of less than 100 mg per deciliter. A multivariate model, adjusted for age, family history of diabetes, body-mass index, physical-activity level, smoking status, and serum triglyceride levels, revealed a progressively increased risk of type 2 diabetes in men with fasting plasma glucose levels of 87 mg per deciliter (4.83 mmol per liter) or more, as compared with those whose levels were in the bottom quintile (less than 81 mg per deciliter [4.5 mmol per liter], P for trend <0.001). In multivariate models, men with serum triglyceride levels of 150 mg per deciliter (1.69 mmol per liter) or more, combined with fasting plasma glucose levels of 91 to 99 mg per deciliter (5.05 to 5.50 mmol per liter), had a hazard ratio of 8.23 (95 percent confidence interval, 3.6 to 19.0) for diabetes, as compared with men with a combined triglyceride level of less than 150 mg per deciliter and fasting glucose levels of less than 86 mg per deciliter (4.77 mmol per liter). The joint effect of a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more and a fasting plasma glucose level of 91 to 99 mg per deciliter resulted in a hazard ratio of 8.29 (95 percent confidence interval, 3.8 to 17.8), as compared with a body-mass index of less than 25 and a fasting plasma glucose level of less than 86 mg per deciliter.

CONCLUSIONS

Higher fasting plasma glucose levels within the normoglycemic range constitute an independent risk factor for type 2 diabetes among young men, and such levels may help, along with body-mass index and triglyceride levels, to identify apparently healthy men at increased risk for diabetes.

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THE DEFINITION OF A NORMAL FASTING plasma glucose level has recently been revised by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association. An impaired fasting plasma glucose level is now considered to include the range of 100 to 109 mg per deciliter (5.55 to 6.05 mmol per liter).[1] Although it raises considerable controversy regarding the implications for health care policy,[2-6] the concept that persons with fasting plasma glucose levels of 100 to 109 mg per deciliter are at increased risk for the development of type 2 diabetes, as compared with those with fasting plasma glucose levels of less than 100 mg per deciliter, is substantiated by data.[5,7,8] Nonetheless, the question of whether there is an association between elevated fasting plasma glucose levels within the newly defined normal range and an increased risk of diabetes, and whether this association acts as an independent risk factor for the disease, has not been answered. This issue is particularly important for young adults, in whom the association between fasting plasma glucose levels and diabetes may have been masked in earlier studies that analyzed populations with a wide age range.[8,9] In young adults, the absolute incidence of type 2 diabetes is low, but a marked surge in diabetes-associated morbidity has recently been reported.[10] Better and earlier identification of young adults at risk for the development of diabetes may be warranted, given the success of interventions aimed at delaying the onset of diabetes among high-risk groups.[11-15]

Our investigation, which involved the use of data from the Metabolic, Lifestyle, and Nutrition Assessment in Young Adults (MELANY) study, assessed whether fasting plasma glucose levels can help to identify young, healthy, normoglycemic persons at increased risk for type 2 diabetes.

METHODS

THE MELANY STUDY

The MELANY study has been conducted at the Israel Defense Forces Staff Periodic Examination Center, to which all career service personnel older than 25 years of age are referred every three to five years. A computerized database established in 1992 is the source of data for MELANY, which was designed to investigate risk factors for common diseases in young adults. At each visit to the Staff Periodic Examination Center, participants completed a detailed questionnaire assessing demographic, nutritional, lifestyle, and medical factors. Thereafter, blood samples were drawn after a 14-hour fast and analyzed. A trained medical technician measured height and weight, and a physician at the center performed a complete physical examination. Primary care for all Israel Defense Forces personnel between scheduled visits to the center is obtained at designated military clinics, and all medical information was recorded in the same central database, thereby facilitating ongoing, tight, and uniform follow-up.

The institutional review board of the Israel Defense Forces Medical Corps approved this study on the basis of strict maintenance of participants' anonymity during database analyses. Data from subjects were recorded anonymously, and no individual consent was obtained. The authors are solely responsible for the design of the study, analysis and interpretation of the data, and writing of the manuscript, without any form of censorship or limitation by the Israel Defense Forces.

INCLUSION AND EXCLUSION CRITERIA

Included in the study have been 13,163 men with fasting plasma glucose levels of less than 100 mg per deciliter at their initial Staff Periodic Examination Center visit, for whom follow-up data have been available through either a subsequent scheduled visit or visits (average number of visits per person, 2.5; range, 2 to 6) or from the primary physician for men who have received a diagnosis of diabetes. The ongoing cohort of the MELANY study currently includes 9538 additional men for whom follow-up data are not yet available. Patients were excluded from the study if they had confirmed type 1 or type 2 diabetes at the time of enrollment. Women were not included, since only 11 new cases of diabetes were diagnosed among 1961 normoglycemic women, an insufficient number of incident cases to facilitate meaningful analysis. Glucose-tolerance tests, shown rarely to be impaired in people with fasting glucose levels of less than 100 mg per deciliter,[16] were not performed, a decision consistent with current clinical guidelines for the diagnosis of diabetes in young, asymptomatic, normoglycemic persons.[17]

OUTCOME DEFINITIONS

The diagnosis of type 2 diabetes was defined as the primary end point of the study. All cases of diabetes were diagnosed according to the criteria published by the American Diabetes Association expert com-

mittee.[18] The diagnoses of all 208 new cases of diabetes in the MELANY study were made on the basis of two fasting plasma glucose levels of 126 mg per deciliter (7.00 mmol per liter) or more. Since the diagnostic criteria for diabetes were changed during the follow-up period, all fasting glucose values were revised to identify subjects with fasting plasma glucose levels of 126 to 140 mg per deciliter (7.00 to 7.77 mmol per liter). Of the 208 subjects with diabetes, 26 received a diagnosis before July 1997, and three cases were detected when the new diagnostic criteria were applied to the population already enrolled in the study at that time. During the follow-up period, two patients received a diagnosis of type 1 diabetes and were excluded from the study. An end-point determination was made at each sequential Staff Periodic Examination Center visit according to measurements of fasting plasma glucose. Alternatively, between visits, the diagnosis of diabetes was made by the Israel Defense Forces primary care physician on the basis of the same diagnostic criteria described above.[18] Three army physicians reviewed and confirmed each of the cases before recording them in the central medical corps database.

LABORATORY METHODS

Biochemical analyses of blood were performed on fresh samples in a core laboratory facility that handles 1.2 million samples per year. The laboratory is authorized to perform tests according to the international quality standard ISO-9002. Periodic assessment of quality control (by the British company National External Quality Assessment Service) has been performed on a regular basis. To ensure that venous fasting plasma glucose levels were reliably determined, blood samples were collected in tubes containing sodium fluoride and delivered to the laboratory within two hours. All measured biochemical markers were identified with the use of a BM/Hitachi917 automated analyzer (Boehringer Mannheim). Blood pressure measurements were performed by medical technicians with the use of mercury sphygmomanometers.

STATISTICAL ANALYSIS

We excluded 3784 of the 16,947 young men at enrollment, 403 because of preexisting diabetes and 3381 because of impaired fasting plasma glucose levels (100 mg per deciliter or more). For analysis, we included 13,163 normoglycemic men with baseline fasting glucose levels of less than 100 mg per deciliter. A general linear model was used to assess the age-adjusted means and proportions of the population's characteristics across quintiles of fasting glucose levels and to fit the median of the quintiles as a continuous variable to estimate the trend of variables across quintiles. We conducted a Cox proportional-hazards analysis during each interval of follow-up to estimate the hazard ratios and 95 percent confidence intervals for the development of type 2 diabetes. We added the values for body-mass index (the weight in kilograms divided by the square of the height in meters) and triglyceride levels separately to the age-adjusted model to evaluate the potential role of each as a confounder of the tested association between fasting plasma glucose level and diabetes. In the final multivariate model, we controlled for age, family history of diabetes, body-mass index, serum triglyceride levels, physical-activity level, and smoking status. We tested for effect modification with stratified analyses of body-mass index, triglyceride levels, and family history of diabetes, all of which remained independent risk factors for diabetes in the multivariate model. Interaction terms were computed by modeling the quintile medians as continuous variables. Next, we evaluated the joint risk attributed to fasting plasma glucose levels (categorized according to the bottom two quintiles, the median quintile, and the top two quintiles) with either body-mass index (<25, 25 to 29.9, and ≥30) or with triglyceride levels (<150 or ≥150 mg per deciliter [1.69 mmol per liter]). We calculated the population attributable risk as previously described.[19] All statistical analyses were performed with the use of SAS statistical software, version 8.0.

RESULTS

Data from 13,163 apparently healthy men (mean age, 32 years; range, 26 to 45) with fasting plasma glucose levels of less than 100 mg per deciliter at baseline were analyzed. Age-adjusted values for body-mass index, triglyceride levels, and the proportion of men with a family history of diabetes were more likely to increase across quintiles of fasting glucose levels (Table 1).

During 74,309 person-years (mean follow-up, 5.7 years), there were 208 documented incident cases of type 2 diabetes. Age-adjusted hazard ratios for type 2 diabetes increased across quintiles of fasting plasma glucose levels, reaching 3.05 (95 percent confidence interval, 1.78 to 5.18) for the top quin-

Table 1. Age-Adjusted Baseline Characteristics of 13,163 Men According to Quintiles of Normal Fasting Plasma Glucose Levels.*

Characteristic	Quintile 1 (N=2529)	Quintile 2 (N=2545)	Quintile 3 (N=2598)	Quintile 4 (N=2719)	Quintile 5 (N=2772)	P Value for Trend
Fasting plasma glucose level (mg/dl)						
Mean	76.4±4.5	84.2±1.4	88.6±1.1	92.5±1.1	96.9±1.4	—
Median	78	84	89	92	97	—
Range	50–81	82–86	87–90	91–94	95–99	—
Age (yr)	32.4±4.6	32.6±4.8	32.5±4.7	32.6±4.8	33.0±4.7	<0.001
Triglyceride level (mg/dl)						
Median	96	99	103	109	116	<0.001
25th, 75th percentile	66, 138	69, 148	72, 153	76, 162	78, 171	
HDL cholesterol level (mg/dl)	46.5±21.6	45.5±20.7	45.7±20.9	45.5±20.9	44.9±21.4	0.05
Total cholesterol:HDL cholesterol ratio	4.9±3.1	5.0±2.9	5.2±2.9	5.2±2.9	5.3±3.0	<0.001
Blood pressure (mm Hg)						
Systolic	118.3±13.0	119.2±12.9	119.3±13.0	119.9±13.0	120±13.0	<0.001
Diastolic	76.2±9.5	76.8±9.4	76.8±9.5	77.2±9.5	77.2±9.5	<0.001
Body-mass index	25.0±3.9	25.3±3.8	25.5±3.9	25.6±3.9	25.9±3.9	<0.001
Family history of diabetes (%)†	16.8	17.7	16.5	18.6	19.6	0.03
Smoking status (%)						
Current	34.9	32.4	31.3	32.6	33.1	0.25
Former	19.5	19.4	19.4	19.3	20.9	0.34
Physical activity (%)‡	11.8	13.0	13.5	12.0	11.3	0.21
Activity index (min/wk)§	153.0	151.0	156.0	152.0	152.0	0.96
Mean follow-up (yr)	5.5	5.5	5.7	5.8	5.9	0.03

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† A family history of diabetes indicates the presence of type 2 diabetes in a first-degree relative.
‡ Physical activity denotes engagement in physical activity for a minimum of 20 minutes at least three times per week.
§ The activity index is the number of reported minutes of physical activity per week among subjects who engaged in physical activity.

tile as compared with the bottom quintile (P for trend <0.001) (Table 2). Further adjustments for body-mass index and triglyceride levels only mildly attenuated the risk values. In a multivariate model adjusted for age, family history of diabetes, body-mass index, serum triglyceride levels, physical activity, and smoking status, we observed a significant and progressive increase in the risk of diabetes in men with fasting plasma glucose levels in the third, fourth, and fifth quintiles as compared with the bottom quintile (P for trend <0.001) (Table 2). This association remained unchanged after further adjustment for blood pressure and for the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, as well as after a secondary analysis that excluded 27 subjects who had received a diagnosis of diabetes within the first two years of follow-up (data not shown).

The addition of fasting plasma glucose levels to a model adjusted for age, body-mass index, family history of diabetes, smoking status, the presence or absence of hypertension, physical-activity level, triglyceride levels, and ratio of total cholesterol to HDL cholesterol further improved the prediction model (P<0.001 on the basis of the likelihood-ratio test).

In the multivariate model, serum triglyceride levels and family history of diabetes, in addition to fasting plasma glucose levels and body-mass index, remained independent risk factors for the development of diabetes (data not shown). Thus, we further assessed the association between fasting plasma glucose levels and the occurrence of type 2 diabetes among strata of these independent risk factors (Table 3). In the multivariate models, increased levels of normal fasting plasma glucose were more strongly associated with diabetes among

Table 2. Hazard Ratios for Type 2 Diabetes among 13,163 Men According to Quintiles of Normal Fasting Plasma Glucose Levels.*

Variable	Quintile 1 (N=2529)	Quintile 2 (N=2545)	Quintile 3 (N=2598)	Quintile 4 (N=2719)	Quintile 5 (N=2772)	P Value for Trend
Fasting plasma glucose levels (mg/dl)	50–81	82–86	87–90	91–94	95–99	—
Person-years of follow-up	13,830	13,969	14,631	15,637	16,242	—
No. of incident cases of diabetes	20	24	37	50	77	—
Adjusted risk ratio (95% CI)						
Age	1	1.47 (0.97–2.23)	1.81 (1.16–2.83)	2.33 (1.42–3.83)	3.05 (1.78–5.18)	<0.001
Age and body-mass index	1	1.35 (0.89–2.05)	1.65 (1.06–2.58)	2.17 (1.32–3.56)	2.68 (1.57–4.56)	<0.001
Age, triglyceride level, and body-mass index	1	1.30 (0.86–1.99)	1.58 (1.02–2.48)	2.05 (1.25–3.37)	2.40 (1.40–4.11)	<0.001
Multivariate†	1	1.43 (0.94–2.19)	1.82 (1.16–2.86)	2.64 (1.60–4.37)	2.84 (1.67–4.87)	<0.001

* CI denotes confidence interval. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† The multivariate Cox regression model was adjusted for age, body-mass index, and triglyceride levels as continuous variables; physical activity (≤60 or >60 minutes per week or missing information); family history of diabetes (positive, negative, or missing information); and smoking status (never smoked, former smoker, current smoker, or missing information).

Table 3. Stratified Analysis of Multivariate Hazard Ratios for Type 2 Diabetes among 13,163 Men According to Quintiles of Normal Fasting Glucose Plasma.*

Variable	Hazard Ratio (95% CI)					P Value for Trend	P Value for Interaction
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Body-mass index†							
<25	1	1.48 (0.52–4.23)	1.64 (0.54–5.29)	1.71 (0.73–6.42)	1.73 (0.79–6.60)	<0.001	0.03
≥25	1	1.36 (0.86–2.15)	1.66 (1.02–2.68)	2.44 (1.43–4.16)	3.78 (1.95–7.35)	<0.001	
Triglyceride level							
<150 mg/dl	1	1.21 (0.63–2.29)	1.50 (0.76–2.97)	2.43 (1.14–5.23)	2.73 (1.28–6.67)	<0.001	0.87
≥150 mg/dl	1	1.41 (0.80–2.49)	1.90 (1.03–3.51)	2.37 (1.25–4.50)	3.24 (1.48–7.10)	<0.001	
Family history							
Negative	1	1.24 (0.66–2.35)	1.50 (0.78–2.87)	3.77 (1.62–8.77)	6.49 (2.25–18.86)	<0.001	0.37
Positive	1	1.96 (0.77–5.02)	2.51 (0.88–7.19)	2.57 (0.94–6.99)	4.58 (1.58–13.33)	<0.001	

* The Cox regression analysis was adjusted, if not stratified, for age, body-mass index, and triglyceride levels, as continuous variables; physical activity (≤60 or >60 minutes per week or missing information); family history of diabetes (positive, negative, or missing information); and smoking status (current smoker, non-current smoker, or missing information). When stratified according to a value of less than 25 or 25 or more, body-mass index was adjusted as a continuous variable within each stratum. CI denotes confidence interval.
† The median of the distribution for body-mass index was found to be 25; therefore, this value was used as the cutoff point for stratification.

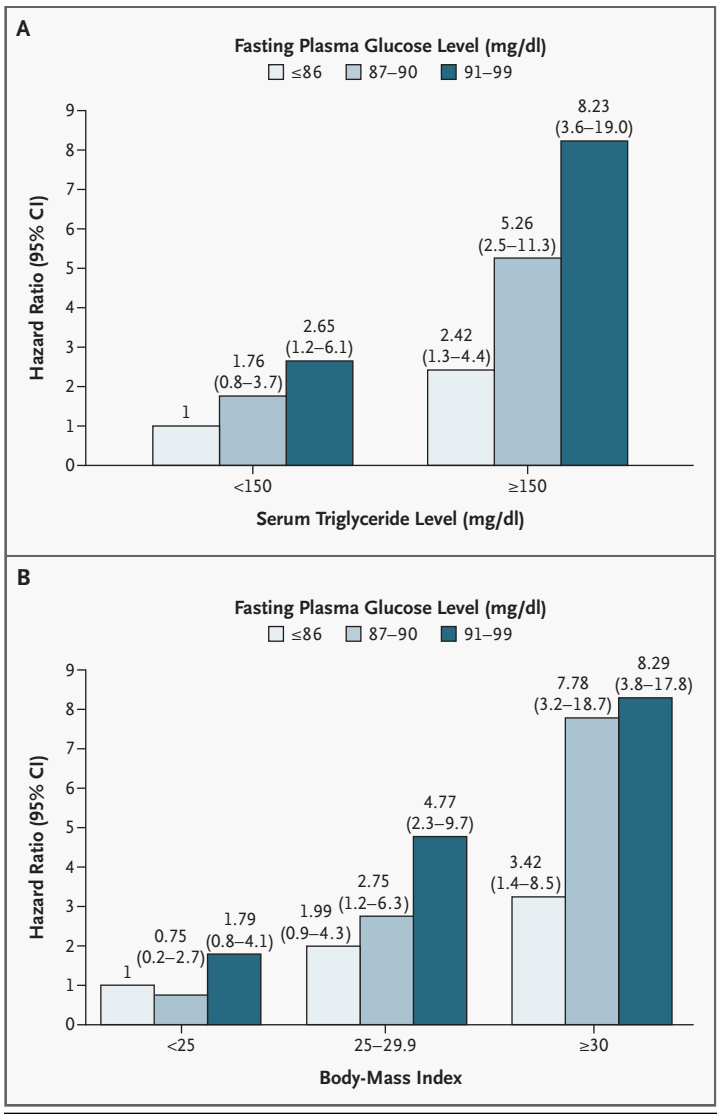

Figure 1. Joint Effect of Fasting Plasma Glucose Levels, Triglyceride Levels, and Body-Mass Index in Predicting Type 2 Diabetes among 13,163 Men.

Panel A shows the hazard ratios for diabetes according to fasting plasma glucose and triglyceride levels. The number of new cases of diabetes that were detected in each of the fasting plasma glucose groups, according to the two triglyceride levels (<150 and ≥150 mg per deciliter, respectively), are as follows: a fasting plasma glucose level of 86 mg per deciliter or less, 20 of 3821 subjects and 30 of 1595; a level of 87 to 90 mg per deciliter, 37 of 2779 and 20 of 592; and a level of 91 to 99 mg per deciliter, 40 of 2997 and 61 of 1379. Panel B shows the relative risk according to body-mass index. The number of new cases of diabetes detected in each group according to body-mass index (less than 25 [lean], 25 to 29.9 [overweight], or higher than 30 [obese]), respectively, were as follows:a fasting plasma glucose level of 86 mg per deciliter or less, 11 of 2511 subjects, 23 of 2057, and 13 of 506; a level of 87 to 90 mg per deciliter, 5 of 1177, 18 of 1129, and 17 of 292; and a level of 91 to 99 mg per deciliter, 19 of 2292, 64 of 2528, and 38 of 671. The multivariate model was adjusted, if not stratified, for age, body-mass index, and triglyceride levels as continuous variables; physical activity (≤60 or >60 minutes per week or missing information); family history of diabetes (positive, negative, or missing information); and smoking status (current smoker, non-current smoker, or missing information). CI denotes confidence interval.

overweight and obese men (those with a body-mass index of 25 or more) than among leaner men (P for interaction, 0.03). The trend of increased risk of type 2 diabetes across increasing quintiles of normal fasting plasma glucose levels appeared to be similar among subgroups classified according to triglyceride levels and family-history status (P for interaction >0.05).

We assessed the joint effect of fasting plasma glucose levels and either triglyceride levels or body-mass index on the risk of type 2 diabetes. In multivariate models, serum triglyceride levels of 150 mg per deciliter or more were associated with an increased risk of diabetes in each category of fasting plasma glucose levels, as compared with the risk in the respective low-serum-triglyceride group (Fig. 1A). Men with fasting plasma glucose levels at the high end of the normal range (91 to 99 mg per deciliter [5.05 to 5.50 mmol per liter]) and serum triglyceride levels of 150 mg per deciliter or more had a risk of 8.23 (95 percent confidence interval, 3.6 to 19.0) for the development of diabetes, as compared with those with fasting glucose levels of 86 mg per deciliter (4.77 mmol per liter) or less and triglyceride levels of less than 150 mg per deciliter. When we cross-classified body-mass index with fasting plasma glucose levels, we observed that each risk factor enhanced the association of the other factor with type 2 diabetes (Fig. 1B). Obese men (those with a body-mass index of 30 or more) with fasting plasma glucose levels in the high-normal range had a hazard ratio of 8.29 (95 percent confidence interval, 3.8 to 17.8) for the development of diabetes, as compared with the reference group, whereas those with fasting plasma glucose levels between 87 and 90 mg per deciliter had a risk of 7.78 (95 percent confidence interval, 3.2 to 18.7). The joint effect of obesity and fasting plasma glucose levels was also apparent in the population attributable risk. Among

lean men, 27.5 percent of cases of diabetes could be prevented by modifying the risk attributable to elevated fasting plasma glucose levels, and in men with the lowest range of fasting plasma glucose levels, 29.1 percent of cases could be attributed to obesity. The combined, population attributable risk increased to 60.5 percent among men with the highest values for both body-mass index and fasting plasma glucose levels, as compared with the reference group.

DISCUSSION

In this follow-up study of 13,163 apparently healthy young adult men, we found an increased risk of type 2 diabetes across quintiles of fasting plasma glucose levels within the newly defined normal range; this increase was independent of other traditional risk factors for diabetes. Our findings suggest that among young adults, who generally have a relatively low incidence of diabetes, elevated normal fasting plasma glucose levels may predict type 2 diabetes.

Several limitations of this study warrant consideration. First, the MELANY cohort may be considered representative of a unique group of healthy young men. However, the characteristics of the population are strikingly similar to those of cohorts in published studies of young men from various industrialized countries,[20-24] and the relatively homogeneous environment to which participants in our study were exposed might reduce the effect of unknown confounders. Second, although they did not compromise the outcome definition, measurements of circulating insulin, C-peptide, or both were not obtained in this study, limiting our ability to assess the role of insulin resistance in the association between normal fasting plasma glucose levels and diabetes. Finally, we did not measure glycosylated hemoglobin levels or perform glucose-tolerance tests. Although the current definition of normal fasting plasma glucose levels resulted in a substantial increase in the overlap with normal glucose tolerance, as defined by glucose-tolerance testing,[8] we may have missed men with normal fasting plasma glucose levels who were already glucose intolerant at enrollment. To limit this possibility, we confirmed our results by performing a secondary analysis in which a two-year lag between enrollment and outcome was used. The strengths of the MELANY study include the detailed, uniform, and systematic follow-up and outcome definition; the use of measured (rather than reported) values for the body-mass index; the availability of reliable determinations of glucose levels in fresh venous blood; and the direct measurements of lipids.

The identification of a high-normal fasting plasma glucose level as a risk factor for type 2 diabetes may help to identify young, healthy men for whom preventive interventions might be considered. Indeed, a number of strategies, including lifestyle modification[14] and medications such as metformin,[14] thiazolidinediones,[13] acarbose,[11,12] and orlistat[15] have been reported as efficient interventions that may delay the onset of diabetes in selected groups that have classic risk factors for the disease. If such strategies are also found to be efficacious in preventing diabetes in young men with high-normal fasting plasma glucose levels, the findings of our study may facilitate efforts to halt the diabetes pandemic that is increasingly affecting people in the third to fifth decades of life.[10]

An impaired fasting plasma glucose level is a known risk factor for diabetes, along with other traditional risk factors such as a family history, sedentary lifestyle, central adiposity, dyslipidemia, and hypertension.[25] However, the definition of a normal fasting plasma glucose level was recently revised to be less than 100 mg per deciliter.[2] It is interesting to note that a few studies have reported the absence of a threshold in the association between fasting plasma glucose levels and the risk of diabetes in cohorts with a wide age range. Furthermore, a fasting plasma glucose level of 94 mg per deciliter (5.22 mmol per liter) was suggested as an optimal point of specificity and sensitivity for predicting type 2 diabetes.[8,9] Our results suggest that in young men, fasting plasma glucose levels within the normoglycemic range can predict type 2 diabetes. Consistent with our findings is the observation that elevated fasting plasma glucose levels within the normoglycemic range can predict cardiovascular, cerebrovascular, and overall mortality risks in persons 45 years of age or older.[26,27] Thus, subcategories within the range defined as normal for fasting plasma glucose levels contain information relevant for the assessment of the risk of various diseases,[28,29] as indicated here for type 2 diabetes.

More than half of the entire study population had fasting plasma glucose levels exceeding 90 mg per deciliter (5.00 mmol per liter), which were associated with a significantly increased risk of diabetes during the mean follow-up of nearly six years. The absolute incident risk of type 2 diabetes among

men who had fasting plasma glucose levels of 91 to 99 mg per deciliter was 2.3 percent during this follow-up period. Therefore, designating a fasting plasma glucose level of more than 90 mg per deciliter as the sole marker of imminent diabetes is unlikely to be useful. Alternatively, the use of an individualized definition of a normal fasting plasma glucose level, which incorporates the compound effect observed with body-mass index and triglyceride levels (Fig. 1), may prove to be of greater clinical value. Indeed, among normoglycemic obese subjects with fasting plasma glucose levels of more than 90 mg per deciliter, the incidence of diabetes was 5.7 percent, as compared with 0.4 percent in lean men with glucose levels of 86 mg per deciliter or less. On the basis of population attributable risk, 60.5 percent of the cases might be preventable by a joint reduction in the risks associated with obesity and high-normal fasting plasma glucose levels. Risk stratification for the definition of normoglycemia is reminiscent of the current guidelines for antidyslipidemic and antihypertensive interventions.[30]

Our study raises potential testable hypotheses with regard to mechanisms. The fasting plasma glucose level is largely determined by hepatic glucose production.[31] Thus, the observation that a high-normal fasting plasma glucose level predicts type 2 diabetes suggests that a relative overproduction of hepatic glucose already exists early in the natural history of diabetes and is exaggerated by obesity (Fig. 1B). Obese persons who do not have diabetes consistently exhibit an enhanced rate of glucose production.[32] This enhanced rate may emanate from elevated levels of free fatty acids that directly accelerate the rate of hepatic gluconeogenesis,[33] combined with desensitization of the hepatic regulatory loop involving hypothalamic sensing of fatty acids.[34] Obesity-associated altered secretion of adipocytokines from adipocytes, macrophages in fat tissue, or both has been suggested as the mechanism involved in mediating such dysregulated "crosstalk" between fatty tissue and the liver.[35-38] Understanding the operative mechanisms that regulate fasting plasma glucose levels may bring us closer to finding new and effective measures to prevent type 2 diabetes in young adults.

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APPENDIX

The following are members of the Israeli Diabetes Research Group Investigators, all in Israel: *Soroka Medical Center, Beer-Sheva* — I. Harman-Bohem; *Hillel Yaffe Medical Center, Hadera* — A. Jaffe; *Rambam Medical Center, Haifa* — E. Karnieli and N. Shehadeh; *Lin Medical Center, Haifa* — O. Minuchin; *Wolfson Medical Center, Holon* — J. Wainstein; *A. Clalit Health Services, Jaffa* — E. Stern; *Hadassah–Hebrew University Hospital, Jerusalem* — B. Glaser and I. Raz; *Clalit Health Services, Jerusalem* — A. Tsur; *Western Galilee Hospital, Nahariya* — T.A. Herskovits; *Sheba Medical Center, Tel-Hashomer* — O. Kalter-Leibovici; *Kaplan Medical Center, Rehovot* — H. Knobler; *Assaf Harofeh Medical Center, Zerifin* — A. Buchs and M. Rapoport; *Maccabi Healthcare Services, Rishon-Le-Ziyon* — J. Cohen; *Souraski Medical Center, Tel-Aviv* — A. Robinshtein; *Clalit Health Services, Tel-Aviv* — Y. Yerushalmy.

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