Predictive Properties of Impaired Glucose Tolerance for Cardiovascular Risk Are Not Explained by the Development of Overt Diabetes During Follow-Up

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OBJECTIVE — To evaluate the relationship of impaired glucose tolerance (IGT) at baseline to coronary heart disease (CHD) incidence, and cardiovascular disease (CVD) and total mortality at follow-up, and to analyze whether the relationship is independent of the subsequent development of diabetes during follow-up.

RESEARCH DESIGN AND METHODS — A baseline screening survey for diabetes was performed in 1987 using a 2-h 75-g oral glucose tolerance test. A total of 1,234 men and 1,386 women aged 45–64 years, who were free of diabetes at baseline, were followed up for 10 years. During the follow-up, 153 subjects had an incident CHD event, 224 died, and 100 deaths were due to cardiovascular causes. Multivariate adjusted (adjusted for age, sex, waist-to-hip ratio, systolic blood pressure, cholesterol, HDL cholesterol, and smoking) hazard ratio (HR) was estimated using Cox regression analysis.

RESULTS — In subjects who had IGT at baseline and who did not progress to diabetes during the follow-up, the multivariate adjusted HR (95% CI) was 1.49 (0.95–2.34) for CHD incidence, 2.34 (1.42–3.85) for CVD mortality, and 1.65 (1.13–2.40) for all-cause mortality.

CONCLUSIONS — Baseline IGT was an independent risk predictor for cardiovascular morbidity and mortality and for total mortality, which was not confounded by the subsequent development of overt diabetes.

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The term "impaired glucose tolerance" (IGT) was originally introduced by the National Diabetes Data Group in 1979 to replace the terms of "borderline diabetes," "latent diabetes," and other categories of glucose intolerance (1). The definition was based on the evidence that subjects with IGT did not appear to have an increased risk of microvascular disease but were at high risk of developing overt diabetes and might be associated with an increased risk for cardiovascular disease (CVD) and death (1).

During the last 20 years, a number of studies have shown that the prevalence of CVD (2–4) as well as mortality from CVD and all causes (5–7) is higher in subjects with IGT than in those with normal glucose tolerance (NGT). Recently, with the revision of the diagnostic criteria for diabetes and milder degree of hyperglycemia, there is an increased interest in the relationship between nondiabetic glucose levels and CVD risk. The Funagata Diabetes Study revealed that IGT doubled the risk of CVD death compared with NGT, but the risk associated with impaired fasting glucose (IFG) did not increase compared with normal fasting glucose (NFG) (8). In the Hisayama Study, the multivariate adjusted hazard ratio for incident stroke and coronary heart disease (CHD) among Japanese subjects with IGT was 1.9 (95% CI 1.2–3.2) compared with those with NGT (9). A collaborative data analysis of 6,766 subjects from five Finnish cohorts showed that the survival profile for CHD incidence and CVD mortality was similar for IGT as for newly diagnosed diabetes, which was worse than that for IFG (10). Analysis of the large DECODE (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) database showed that IGT was a risk predictor for mortality from all causes, CVD, and non-CVD, independent of fasting glucose levels and other known CVD risk factors such as age, sex, BMI, systolic blood pressure, total cholesterol, and smoking; the largest absolute number of deaths was observed in subjects with IGT, especially in those with IGT but NFG (11,12). However, in all these previous studies, IGT was defined only at baseline, and possible deterioration in glucose tolerance from IGT to diabetes during follow-up was not taken into account. Studies have recently reported that the risk of developing diabetes is higher in subjects with either IFG or IGT, with the highest risk in those with both IFG and

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; FBG, fasting whole blood glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MI, myocardial infarction; NFG, normal fasting glucose; NGT, normal glucose tolerance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

IGT, as compared with subjects with NFG and NGT (13–16). Therefore, it is important to assess whether the increased CVD risk related to baseline IGT is attributed to the development of diabetes during follow-up and to what extent the concurrent presence of IFG confounds the relation. This is now investigated in a Finnish cohort.

RESEARCH DESIGN AND METHODS

Baseline survey in 1987

The study cohort was recruited in 1987 from the national population register of the defined geographic areas of Finland for the FINMONICA study (17,18). The prevalence of diabetes was investigated by asking a random sample of 1,654 men and 1,750 women aged 45–64 years questions on history of diabetes and by screening them with a 2-h 75-g oral glucose tolerance test. Of the eligible subjects in the sample, 81% attended the oral glucose tolerance test at baseline. Blood samples were collected from 1100 to 1600 after fasting for at least 4 h, and 2-h blood samples were drawn 2 h after a 75-g oral glucose load (19). The mean fasting time was 6.8 h for the participants. Whole blood glucose was determined in the central laboratory with a hexokinase-glucose-6-phosphate dehydrogenase method. Measurements of weight, height, waist and hip circumferences, and blood pressure at baseline were made according to the standard MONICA project procedures described elsewhere in detail (17,18).

Subjects with a prior history of diabetes or newly diagnosed diabetes at the baseline screening based on fasting whole blood glucose (FBG) ≥6.1 mmol/l and/or 2-h whole blood glucose ≥10.0 mmol/l (20) were excluded from the current data analysis. A total of 2,535 subjects (1,178 men and 1,357 women) aged 45–64 years, who were free of diabetes at baseline and who also had data on waist-to-hip ratio, blood pressure, cholesterol, HDL cholesterol, and smoking, were classified as having IFG and NFG based on the FBG of 5.6–6.0 and <5.6 mmol/l, respectively. A 2-h whole–blood glucose level of 6.7–9.9 and <6.7 mmol/l defined IGT and NGT.

Follow-up study until 1997

Definition of clinically diagnosed diabetes. Data on clinically diagnosed diabetes were obtained by computerized record linkage of the unique national identification numbers assigned to every Finnish resident. The survey participants were linked to the national Drug Register of Social Insurance Institution and the national Hospital Discharge Register for incidence of overt diabetes. Thus, the follow-up was complete with no loss. The *International Classification of Diseases* (ICD), *Ninth Revision*, was used for the classification of the events: ICD codes 250.0–250.9 (E11–E11.9) were used to identify people with type 2 diabetes. The Social Insurance Institution provides free-of-charge medication to all patients with diabetes in Finland after an approval procedure that requires a detailed clinical statement from the treating physician. Also, a treatment period of at least 6 months with nonpharmacological means is required before the reimbursement of drugs is endorsed. Therefore, the drug register comprises information about all Finnish people who have been approved to receive free-of-charge drug treatment for diabetes.

Definition of CHD incidence and CVD events. The definition of CHD events was made based on clinical symptoms, electrocardiogram findings, cardiac enzymes, necropsy findings, and previous history of CHD. In the present analysis, we used ICD codes 410–414 (I20–I25) for fatal CHD, 410–411 (I21–I22, I24) for nonfatal acute myocardial infarction (MI), and 401–448 (I10–I79) for total fatal cardiovascular events. Incident CHD category was defined to comprise the first-ever events of CHD death or nonfatal MI. Subjects with previous MI at baseline were excluded from the calculations of the incidence of CHD events, leaving 2,457 subjects (1,119 men and 1,338 women) for the study of incident CHD.

Validity of the registration data. The data for CHD incidence and mortality were obtained from the National Cause-of-Death Register (Statistics Finland) and the National Hospital Discharge Register. The quality of the registration data has been assessed previously against the FINMONICA MI register (21,22). The assessment revealed that 94% (95% CI 92–96%) of the CHD events (nonfatal MI and fatal CHD together) recorded in the routine National Registers were defined as either definite or possible CHD by the FINMONICA MI Register (21). Only 1.7% of the CHD death in men and 4.8% in women did not fulfil the FINMONICA criteria for CHD death (22). Therefore, the diagnoses of MI and death from CHD in the routine National Registers were highly predictive of a true major coronary event defined by strict criteria, and their use in end-point assessment in epidemiological studies and clinical trials is justified (21,22).

Statistical analysis

The 10-year incidence of CHD and mortality were calculated as the number of subjects who developed the events of interest during the follow-up divided by the duration of follow-up. Hazard ratios for CHD incidence and mortality were estimated using the Cox proportional hazards analysis. Adjustment was made first for age and sex, and then additional adjustments for BMI, waist-to-hip ratio, systolic blood pressure, cholesterol, HDL cholesterol, and smoking status of nonsmoker, ex-smoker, and current smoker were performed. BMI was not included in the final model because addition of BMI to the model based on the other risk factors above did not improve the prediction. Hazard ratios and their 95% CIs are reported.

All the data analyses were performed separately for subjects with and without diabetes diagnosed during follow-up. For those who did not develop overt diabetes during follow-up, further stratified analyses were carried out for categories of IGT and NGT. Because of the low prevalence of IFG (0.7%, 18/2,535) at baseline, data analysis was not made separately for IFG. Of the 18 subjects with IFG, 1 developed overt diabetes during the follow-up and was classified as diabetic. Of the 17 IFG subjects who were free of overt diabetes at the end of follow-up, 13 were classified into the NGT category and 4 into the IGT category according to their 2-h whole–blood glucose levels.

RESULTS — Among the 2,457 subjects who were free of diabetes and CHD at baseline, 97 (3.9%) developed overt diabetes during the 10-year follow-up. For these 97 diabetic subjects, their baseline classifications were as follows: 54 (56%) in the group with NFG and NGT, 42 (43%) with NFG and IGT, and 1 (1%) with IFG and IGT. Men had a slightly

Table 1—*Baseline characteristics of subjects who were free of diabetes and CHD at baseline*

	Nondiabetic at follow-up		Diabetic at follow-up	*P**
Baseline 2-h glucose (mmol/l)	<6.7	6.7–9.9	<10.0	—
n (%)	2,110 (85.9)	250 (10.2)	97 (3.9)	—
Men (%)	46.3	37.2	51.5	0.012
Age (years)	53 ± 0.1	56 ± 0.4	56 ± 0.6	<0.001
BMI (kg/m^2)	27.3 ± 0.1	28.7 ± 0.3	31.3 ± 0.4	<0.001
Waist-to-hip ratio				
Men	0.92 ± 0.002	0.94 ± 0.006	0.97 ± 0.009	<0.001
Women	0.79 ± 0.002	0.81 ± 0.005	0.83 ± 0.008	<0.001
Systolic blood pressure (mmHg)	146 ± 0.4	151 ± 1.2	154 ± 2.0	<0.001
Diastolic blood pressure (mmHg)	88 ± 0.2	89 ± 0.7	92 ± 1.1	<0.001
Cholesterol (mmol/l)	6.4 ± 0.03	6.7 ± 0.08	6.5 ± 0.12	0.004
HDL cholesterol (mmol/l)	1.5 ± 0.01	1.4 ± 0.02	1.2 ± 0.03	<0.001
Current smokers (%)	19.5	10.0	17.5	<0.001

Data are age- and sex-adjusted means ± SE unless otherwise indicated. The subjects are grouped according to the baseline 2-h glucose categories, stratified by diabetes status at follow-up. *Tested using ANOVA or the χ^2 test.

higher incidence of diabetes than women (Table 1). Diabetic subjects had the worst CVD risk profiles among the study groups. People with IGT had the risk profiles between the normal glucose tolerant and diabetic subjects.

The CHD incidence and mortality from CVD and all causes was increased in subjects with IGT and in those with overt diabetes (Table 2). After multivariate adjustment for the CVD risk factors assessed, the risk of CHD incidence was still 49% higher in subjects with IGT at baseline and 79% higher in those who developed overt diabetes during follow-up, as compared with people who had normal glucose tolerance (Table 2).

CONCLUSIONS — It has been previously speculated that the risk of CVD associated with IGT might be explained by the fact that people with IGT are at high risk of developing diabetes. Our study demonstrated that IGT at baseline is an independent risk predictor for the incidence of CHD and premature death from CVD and all causes, which was not confounded by the development of clinically diagnosed diabetes during the follow-up. To our knowledge, this is the first time the relation between IGT and CVD risk was studied, controlling for the diabetic status at the end of follow-up. Earlier studies have shown that people who develop type 2 diabetes have increased levels of several CVD risk factors before becoming diabetic (23–25). The cluster of risk factors in subjects with IGT may explain the increase in the number of CVD events associated with IGT. Indeed, in our study, the CVD risk profiles also deteriorated linearly with the conversion from NGT to

Table 2—*Ten-year incidence of CHD, cardiovascular and all-cause mortality, and the corresponding hazard ratios, according to baseline 2-h glucose categories stratified by diabetic status at follow-up in subjects free of diabetes at baseline*

	Nondiabetic at follow-up		Diabetic at follow-up
Baseline 2-h glucose (mmol/l)	<6.7	6.7–9.9	<10.0
CHD incidence			
n (%)	2,110 (85.9)	250 (10.2)	97 (3.9)
n (rate per 1,000 person-years)	114 (5.3)	24 (9.7)	15 (16.1)
Age- and sex-adjusted HR (95% CI)	1	1.72 (1.11–2.69)	2.45 (1.43–4.21)
Multivariate-adjusted HR (95% CI)*	1	1.49 (0.95–2.34)	1.79 (1.02–3.16)
Cardiovascular mortality			
n (%)	2,173 (85.7)	262 (10.3)	100 (3.9)
n (rate per 1,000 person-years)	70 (3.1)	21 (7.9)	9 (8.7)
Age- and sex-adjusted HR (95% CI)	1	2.51 (1.53–4.10)	2.29 (1.14–4.60)
Multivariate-adjusted HR (95% CI)*	1	2.34 (1.42–3.85)	1.69 (0.82–3.47)
Total mortality			
n (%)	2,173 (85.7)	262 (10.3)	100 (3.9)
n (rate per 1,000 person-years)	174 (7.6)	34 (12.8)	16 (15.5)
Age- and sex-adjusted HR (95% CI)	1	1.61 (1.11–2.34)	1.71 (1.02–2.86)
Multivariate-adjusted HR (95% CI)*	1	1.65 (1.13–2.40)	1.50 (0.88–2.54)

*Adjusted for age, sex, waist-to-hip ratio, systolic blood pressure, cholesterol, HDL cholesterol, and smoking. HR, hazard ratio.

IGT and to overt diabetes. The higher the glucose levels, the poorer the CVD risk profiles. However, the adjustment for risk factors other than age and sex only lowered the hazard ratio for CHD from 1.72 (age and sex adjustment only) to 1.49 (additional adjustment for other CVD risk factors), accounting for 23% of the increment in CHD risk associated with IGT. And the multivariate adjustment did not change the hazard ratios for the total mortality. This suggests that IGT per se is a risk factor for increased CVD morbidity and mortality, and hyperglycemia may be directly involved in the development of CVD. Recently, Ceriello et al. (26) showed an independent and cumulative deleterious effect of both postprandial hypertriglyceridemia and 75-g postload hyperglycemia on endothelial function and suggested that oxidative stress is the common mediator through which they exert such an effect. From the public health perspective, it is important to target a prevention program at people with IGT to reduce the incidence of diabetes (27–29) and to see whether a reduction in CVD morbidity and mortality will also result.

It could also be argued that the relation between IGT and cardiovascular events might as well have been confounded by hypertension or dyslipidemia occurring during the follow-up, taking into account the relatively high baseline levels of systolic blood pressure and cholesterol in the study population. In the middle of the 1980s, the blood pressure and cholesterol levels in this study population were higher compared with the most of the other Caucasian populations, but they decreased in the last decades (30,31). The same decline in CHD and stroke events was also reported (32,33). The clustering of glucose intolerance with hypertension, dyslipidemia, obesity, and insulin resistance has been recognized since 1923 (34,35), but the mechanisms underlying the clustering of the abnormalities are still not fully understood. The data on hypertension and dyslipidemia at the end of the follow-up were not measured in the current study. To what degree the other cardiovascular risk factors confounded the observation cannot be estimated, and further investigation is needed. Nevertheless, the fact that patients with IGT are at high risk for cardiovascular disease cannot be neglected.

One weakness of the current study is that a glucose tolerance test was not performed at the end of follow-up. The patients with asymptomatic undiagnosed diabetes and those on diet treatment only were not identified, resulting in an overestimate of the mortality risk associated with IGT. If this is true, then the risk in subjects with NGT was also overestimated. The relative risk for IGT compared with NGT may not be changed substantially. On the other hand, the clinical definition of diabetes in our study avoided the potential misclassification due to the problem related to the inadequate fasting, glucose load, and reproducibility of the oral glucose tolerance test. In addition, the bias regarding the incident CHD events is small because all these patients were hospitalized and blood glucose measurement is routinely done for them.

The fasting time at the baseline examination was short (on average 6.8 h) and most of the fasting blood samples were collected in the afternoon (19). It has been reported that afternoon fasting glucose values were lower than morning values, but the length of fast was not an important factor (36). We examined the mean values of the baseline fasting and the 2-h glucose concentrations according to the hour of starting the fasting blood sampling. At the hours of ≤1100, 1200, 1300, 1400, and ≥1500, the age- and sex-adjusted mean values for the FBG concentration (in mmol/l) were 4.2, 4.2, 4.1, 4.1, and 4.1, respectively ($P < 0.001$); for 2-h glucose, 4.9, 4.9, 5.2, 5.0, and 4.9, respectively ($P = 0.31$). The mean fasting glucose levels tended to be lower in the afternoon than in the late morning, but 2-h glucose did not. The correlation coefficient between the mean fasting time and the fasting glucose concentration was 0.01 ($P = 0.63$), indicating that the length of the fast was not closely related to the fasting glucose levels in this study population. This is in agreement with the previous findings (36). It would be argued that subjects with diabetic fasting glucose values at baseline would have been misclassified into the nondiabetic category because of the afternoon sampling. However, after 10 years of follow-up, overt diabetes should have been ascertained and could not possibly bias the observations between IGT and CHD. To estimate the potential impact of the afternoon sampling on the outcome events, the crude incidence of clinically diagnosed diabetes and the incidence of CHD were also calculated according to the hours of ≤1100, 1200, 1300, 1400, and ≥1500. The incidences (%) for clinically diagnosed diabetes were 3.8, 3.7, 3.2, 4.6, and 4.0, respectively ($P = 0.88$); for incidence of CHD, 5.3, 8.0, 7.2, 6.1, and 5.0, respectively ($P = 0.23$). The mean ages were 54.0, 54.0, 54.0, 54.0, and 53.1 years, respectively. Therefore, the short fasting time and the afternoon sampling could not bias the study systematically.

We conclude that IGT is an independent risk predictor for CVD morbidity and mortality and for all-cause mortality. This cannot be explained by the subsequent development of overt diabetes.

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