Population-Based Incidence of Type 2 Diabetes in Northern Spain

The Asturias Study

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OBJECTIVE — The aim of this study was to define the incidence of type 2 diabetes in a low-risk Caucasian population in northern Spain and its association with various risk factors.

RESEARCH DESIGN AND METHODS — The Asturias Study is a prospective, population-based survey of diabetes and cardiovascular risk factors. The baseline examination was carried out during 1998–1999 when 1,034 individuals, aged 30–75 years, were randomly selected to determine the prevalence of type 2 diabetes and pre-diabetes in the Principality of Asturias (northern Spain). In 2004–2005, these same subjects were invited for a follow-up examination; 700 participated. This study includes only those individuals who did not have diabetes at baseline. We used the World Health Organization 1999 criteria to classify glucose metabolism at both baseline and follow-up.

RESULTS — The incidence of diabetes adjusted for the age and sex structure of Asturias was 10.8 cases/1,000 person-years (95% CI 8.1–14.8). The incidence rates were 5 cases/1,000 person-years in individuals with normoglycemia, 21 cases/1,000 person-years in individuals with isolated impaired glucose tolerance (IGT), 34.7 cases/1,000 person-years in individuals with isolated impaired fasting glucose (IFG), and 95.2 cases/1,000 person-years in individuals with combined IFG-IGT. Stepwise multiple logistic regression analysis showed that, together with fasting plasma glucose (FPG) and 2-h plasma glucose, which were the strongest predictors of diabetes, triglycerides and BMI were also independently associated with progression to diabetes.

CONCLUSIONS — In this 6-year prospective population-based study, we found an incidence of type 2 diabetes of 10.8 cases/1,000 person-years. Both FPG and 2-h plasma glucose were strongly predictive of diabetes, and their effect was additive.

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Type 2 diabetes is currently one of the most costly and worrying chronic diseases and represents a serious health care problem worldwide. The number of individuals with diabetes is increasing alarmingly owing to the aging of the population, obesity, and lack of exercise. Estimates indicate that by the year 2030 diabetes will affect 366 million people worldwide (1). In practically all societies, diabetes has become a leading cause of blindness, renal failure, lower limb amputation, and cardiovascular disease. The increased prevalence of diabetes has led to an increasing number of disabled individuals, a decrease in life expectancy, and huge health care costs (2). In Spain, too, the situation is a cause for concern, and recent cross-sectional studies indicated an increase in the prevalence of type 2 diabetes that does not appear to be due to changes in the criteria for diabetes (3–13). Therefore, interest in identifying individuals at high risk of developing diabetes and in planning preventive strategies has increased considerably because several studies have demonstrated that diabetes can be prevented with changes in lifestyle and/or use of drugs (14–18).

The incidence of diabetes is strongly related to pre-diabetic dysglycemia, i.e., impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), but the risk varies widely according to the particular population (19) and is poorly documented in Spain. Accordingly, we assessed the incidence of type 2 diabetes in a low-risk Caucasian population from northern Spain and its association with IFG, IGT, and other risk factors.

RESEARCH DESIGN AND METHODS

— The Asturias Study is a prospective population-based survey of diabetes and cardiovascular risk factors. The baseline examination was carried out during 1998–1999 to determine the prevalence of type 2 diabetes and pre-diabetes in the Principality of Asturias in northern Spain. The population of Asturias is 1,073,761 and mostly Caucasian. Approximately half of the population lives in urban areas. A two-step sampling technique was used. Fifteen basic health areas were selected at random from among the 76 in Asturias with a probability proportional to the number of health cards of users aged between 30 and 75 years. A computer program was then used to randomly select 125 individuals in each basic health area. The final sample size selected was 1,875; 87 individuals were excluded for various reasons (type 1 diabetes, pregnancy, severe disease, hospitalization, or use of diabetogenic drugs). Another 162 individuals were excluded because data needed to contact them were missing. The final sample was composed of 1,626 individuals, of whom 1,034 (63.6%) responded. The results showed that 11.3% of all participants had diabetes, 8.9% had isolated IGT, 4.1%

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Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

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

Table 1—*Comparison between participants and nonparticipants in a diabetes incidence study*

	Participants	Nonparticipants	*P* value
n	634	206	
Sex: female/male (%)	56.3/43.7	57.3/42.7	NS
Age (years)	51.5 ± 12.4	49.6 ± 13.8	NS
Population type: rural/medium/urban (%)	23.7/27.8/48.6	20.4/28.2/51.5	NS
Education level: none-basic/high school/college (%)	22.7/61.9/15.3	18/64.9/17.1	NS
Smoking: current/former/never (%)	25.6/11.6/62.8	31.7/12.7/55.6	NS
Family history type 2 diabetes (%)	21.6	21.8	NS
Systolic blood pressure (mmHg)	130.1 ± 19.8	133.7 ± 21.6	0.04
Diastolic blood pressure (mmHg)	82.1 ± 13.2	83.4 ± 13.3	NS
BMI (kg/m²)	27.2 ± 4.4	27.2 ± 4.8	NS
Total cholesterol (mg/dl)	228.2 ± 42.5	227.9 ± 39.5	NS
LDL cholesterol (mg/dl)	149.7 ± 38.4	147.9 ± 35.1	NS
HDL cholesterol (mg/dl)	56.9 ± 14.3	57.3 ± 13.4	NS
Triglycerides (mg/dl)	110.8 ± 70.3	113.3 ± 60	NS
FPG (mg/dl)	94.6 ± 10.0	94.4 ± 10.3	NS
2-h plasma glucose (mg/dl)	104.7 ± 32.0	107.1 ± 32.8	NS

Data are means ± SD or %.

had isolated IFG, and 3.5% had combined IFG-IGT.

Between November 2004 and October 2005 the original participants were invited to participate in a follow-up examination. Vital status and current residency of all individuals were obtained from their health service identification card. Of the original cohort, 42 individuals had died and 19 had left Asturias before the follow-up started. Thirty other individuals were excluded (because of pregnancy, severe disease, hospitalization, or use of diabetogenic drugs). Of the remaining 943 individuals, 700 participated (74.2%). The present study includes only those individuals who did not have diabetes at the baseline.

The study was approved by the local ethics committee. All participants gave informed consent.

Clinical examination

All examinations and analyses were performed at the patients' local health centers by an endocrinologist and a trained nurse. Information on demographic data, smoking habits, physical activity, socioeconomic position, and a family history of diabetes was obtained by questionnaire. Smoking history was derived from yes/no responses to the questions "Have you ever smoked at least 1 cigarette per day for as long as 1 year?" and "Do you smoke cigarettes now?" Information was used to classify subjects as "current," "former," or "never smokers." Self-reported leisure-time physical activity was classified into three categories: "low," almost completely inactive; "moderate," some physical activity >1 h/day, e.g., walking, gardening, dancing, or bicycling; or "high," vigorous physical activity >3 h/week, e.g., running, swimming, ball games, or competitive sports. A family history of diabetes was coded as positive when the subject had one or more first-degree relatives with the disease. The area of residence was classified according to the municipal population: "rural," <10,000 inhabitants; "medium," 10,000–50,000 inhabitants; or "urban," >50,000 inhabitants. Occupation, work status (active/unemployed/retired), education level (none/basic/high school/college), and marital status (single/married/separated/widowed) were also assessed. Medical records were reviewed to investigate previous diseases or medication.

Height, weight, and BMI (weight in kilograms divided by the square of height in meters) were measured with the subject wearing light clothing and without shoes. Blood pressure was measured with a digital sphygmomanometer (OMROM MX3) after several minutes in a seated position; the mean of two measurements taken 1–2 min apart was used for analysis.

Laboratory data

All participants without known diabetes underwent an oral glucose tolerance test (OGTT), both at baseline and at the follow-up, obtaining fasting and 2-h venous samples following the recommendations of the World Health Organization (20). The samples were centrifuged in situ using a portable centrifuge. A portable refrigerator containing the samples was taken daily to the Biochemical Laboratory of the Central Hospital of Asturias. Glucose was determined by the hexokinase enzymatic method (Hitachi 747). The glucometabolic state was classified according to the World Health Organization 1999 criteria: IFG, fasting plasma glucose (FPG) 110–125 mg/dl; IGT, 2-h plasma glucose 140–199 mg/dl; and type 2 diabetes, FPG ≥126 mg/dl and/or 2-h plasma glucose ≥200 mg/dl (20). Additional laboratory measurements included total cholesterol, HDL cholesterol, triglycerides (colorimetric method), LDL cholesterol (Friedewald formula), and A1C (high-performance liquid chromatography, Adams HA-8160). C-reactive protein, insulin, and microalbuminuria were only measured at the follow-up examination and were not included in this analysis.

Statistical analyses

The incidence rate of diabetes in the cohort was calculated, assuming a constant rate of disease over the follow-up and expressed per 1,000 person-years. Adjusted incidence was estimated by the direct method using the total population in Asturias aged 30–75 years according to 1998 census. The strength of association between clinical categories and the development of diabetes was measured by calculating age- and sex-adjusted odds ratios (ORs) by univariate logistic regression analyses. The variables age, sex, education level, family

Table 2—*Six-year incidence rates and ORs for type 2 diabetes according to various clinical categories at baseline*

Clinical categories	No. at risk	No. developing diabetes	Incidence rate/ 1,000 person-years (95% CI)	OR (95% CI)*
Sex				
Female	354	20	9 (5.5–13.8)	1
Male	276	24	13.8 (8.8–20.5)	1.6 (0.9–2.9)
Age				
<45 years	224	12	8.5 (4.4–14.9)	1
45–60 years	218	14	10.2 (6–17.2)	1.2 (0.5–2.7)
≥60 years	188	18	15.2 (9.6–24.1)	1.9 (0.9–4)
Population type				
Urban	307	21	10.9 (6.7–16.6)	1
Medium	176	11	9.9 (5–17.8)	0.9 (0.4–2)
Rural	147	12	13 (6.7–22.6)	1.2 (0.6–2.6)
Education level				
High school/college	487	23	7.5 (4.8–11.2)	1
Basic/none	142	21	23.5 (14.5–35.9)	3.7 (1.8–7.6)
Family history of diabetes				
No	493	30	9.7 (6.5–13.8)	1
Yes	136	14	16.3 (8.9–27.4)	1.9 (1–3.7)
Physical activity				
Moderate–high	441	23	8.3 (5.2–12.4)	1
Low	189	21	17.6 (10.9–27)	2.7 (1.4–5.1)
Smoking				
Former–never	467	33	11.2 (7.7–15.8)	1
Current	161	11	10.8 (5.4–19.4)	1 (0.5–2.2)
Systolic blood pressure ≥140 mmHg				
No	423	18	6.8 (4–10.7)	1
Yes	207	26	19.9 (13–29.2)	2.9 (1.5–5.8)
Diastolic blood pressure ≥90 mmHg				
No	437	16	5.8 (3.3–9.4)	1
Yes	193	28	23 (15.3–33.2)	4 (2.1–7.9)
BMI				
<25 kg/m^2	205	4	3.1 (0.8–7.9)	1
25–30 kg/m^2	277	22	12.6 (7.9–19.1)	3.7 (1.3–11.2)
≥30 kg/m^2	148	18	19.3 (11.4–30.5)	6.1 (2–18.8)
Total cholesterol ≥240 mg/dl				
No	388	21	8.6 (5.3–13.1)	1
Yes	242	23	15.1 (9.6–22.6)	1.6 (0.8–3)
Triglycerides ≥200 mg/dl				
No	583	33	9 (6.2–12.6)	1
Yes	47	11	37.1 (18.5–66.4)	4.8 (2.2–10.4)
HDL cholesterol<40 mg/dl				
No	507	27	8.4 (5.8–12.3)	1
Yes	120	16	21.2 (12.1–34.4)	2.9 (1.5–5.6)
IFG				
No	578	25	6.9 (4.6–10.2	1
Yes	52	19	58 (37–90.9)	11.5 (5.6–23.6)
IGT				
No	542	23	6.7 (4.5–10.1)	1
Yes	88	21	37.9 (24.7–58.1)	6.7 (3.4–13.3)

*Odds ratios are age and sex adjusted.

history of diabetes, physical activity, diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, BMI, FPG, and 2-h plasma glucose were included in a stepwise, multivariate, logistic regression analysis to study their independent prognostic significance. All statistical analyses were performed with SPSS 12.0 and Epibasic 1.0. Reported *P* values are based on two-sided tests with a cutoff for statistical significance of 0.05.

RESULTS — Of the original participants, 905 did not have diabetes at baseline. Of these, 24 had died, 15 had left Asturias before the reevaluation started, and 26 others were excluded (because of pregnancy, severe disease, hospitaliza-

Table 3—*Six-year incidence rates and ORs for type 2 diabetes according to baseline glucose categories: World Health Organization 1999 criteria*

Glucose categories	No. at risk	No. developing diabetes (%)	Incidence rate/1,000 person-years (95% CI)	OR (95% CI)*
Normoglycemia	510	16 (3.1)	5.0 (2.8–8)	1
Isolated IGT	68	9 (13.2)	21 (10.9–40.4)	4.7 (1.9–11.7)
Isolated IFG	32	7 (21.9)	34.7 (14–71.5)	8.4 (3.1–23)
Combined IFG-IGT	20	12 (60)	95.2 (54.1–167.7)	45.6 (15.8–131.4)

*Odds ratios are age and sex adjusted.

tion, or use of diabetogenic drugs). Of the remaining 840 individuals invited to take part in the follow-up study, 634 participated (75.5%). Table 1 shows that there were virtually no differences between participants and nonparticipants for most baseline parameters. Four individuals were excluded from the final analyses because of lack of OGTT data. Thus, the study population included 630 subjects (56.2% female and 43.8% male) with an age range of 30 to 75 years at baseline. The mean follow-up was 6.3 years (range 5.9–6.8 years).

Diabetes incidence rate

In the 630 individuals who completed the study, we found 44 new cases of diabetes (7%). This figure represents a crude incidence of diabetes of 11.2 cases/1,000 person-years (95% CI 8.1–14.8) and an incidence adjusted for the age and sex structure of the Asturian population in this age range of 10.8 cases/1,000 person-years (95% CI 7.8–14.6).

Risk factors for development of type 2 diabetes

Table 2 includes the incidence rates and ORs of various risk factors involved in the etiopathogenesis of type 2 diabetes. The incidence was slightly higher in men than in women and rose with increasing age. We found no significant risk for diabetes according to the area of residence. For socioeconomic position, rather than occupation or work status, which had no associated risk (data not shown), education level was strongly associated with the development of type 2 diabetes, the risk being more than threefold higher in individuals who did not have a high school diploma than for individuals who had received higher education. The risk for diabetes was virtually the same in current smokers as in nonsmokers. Comparison of current and former smokers versus never smokers showed similar results (data not shown). Other variables such as a family history of diabetes, low physical activity, systolic hypertension, diastolic hypertension, obesity, hypertriglyceridemia, and low HDL cholesterol were also associated with the development of diabetes. Both IFG and IGT were highly associated with diabetes. These two groups overlapped, with the risk being moderate in individuals with isolated IFG or isolated IGT and extremely high in individuals with combined IFG-IGT (Table 3).

Stepwise multiple logistic regression analysis showed that, together with FPG and 2-h plasma glucose, which were the strongest predictors of diabetes, triglycerides and BMI were also independently associated with progression to diabetes (Table 4). In a parallel analysis with a fixed model including the same variables, only FPG and 2-h plasma glucose remained significantly predictive of diabetes (both $P < 0.001$).

CONCLUSIONS — In this prospective study, we report the incidence rates of type 2 diabetes and evaluate various risk factors for the development of diabetes in a representative sample of the general population of a whole province in northern Spain, including residents in both urban and rural areas. Cases of diabetes were determined on the basis of an OGTT both at baseline and at follow-up and are thus an approximation of the total figures for diabetes (known + unknown). Although the participation at the follow-up of the original cohort was not complete (75.5%), very few differences existed between participants and nonparticipants, thereby minimizing any possible selection bias.

The incidence rate of type 2 diabetes has not been clearly defined for the European population, mainly because data are lacking. Some studies that determined cases of diabetes based on questionnaires, review of medical records, or use of drugs showed results ranging from 1 to 5 cases/1,000 person-years (21–26). These figures are clearly underestimates, as the studies only included persons who already had a diagnosis of diabetes. Studies based on fieldwork with repeated glucose analysis data are fewer. The only previous reference in Spain is the Lejona Study, in which a cohort of 594 individuals without diabetes at baseline were reevaluated after a follow-up of 10 years. The incidence of diabetes was 8.2 cases/1,000 person-years (27). In Naples, 560 employees of a telephone company (aged 40–59 years) without diabetes were prospectively studied after an initial cross-sectional study. Over a follow-up of 11.5 years, 54 had progressed to diabetes. However, only FPG was determined at the follow-up study (28). In Ely, U.K., a longitudinal study included 937 individuals without diabetes with a mean follow-up of 4.5 years and reported an incidence of 6.2 cases/1,000 person-years (29). The Hoorn Study in Holland evaluated 1,342 nondiabetic individuals at baseline and after a mean of 6.4 years, finding 133 new cases of diabetes, which represents an approximate incidence of 15 cases/1,000 person-years. However, the high age level of the cohort (50–75 years) could account for this high incidence of diabetes (30). In the Bruneck Study (northern Italy), a total of 837 individuals without diabetes were included. After a follow-up of 10 years, 64 had progressed to diabe-

Table 4—*Multivariate logistic regression analyses: variables predictive of diabetes during 6 years of follow-up*

Variable	Wald	SD	OR (95% CI) per SD difference
FPG (mg/dl)	29.8	9.94	2.15 (1.73–2.60)
2-h plasma glucose (mg/dl)	14.6	32.08	1.71 (1.32–2.06)
Triglycerides (mg/dl)	13.3	70.46	1.56 (1.28–1.84)
BMI (kg/m^2)	8.4	4.40	1.54 (1.17–1.94)

Age, sex, education level, physical activity, family history of diabetes, diastolic blood pressure, total cholesterol, and HDL cholesterol were also considered but not included in the final model.

tes. The incidence adjusted to the age and sex structure of Bruneck was 7.6 cases/1,000 person-years. Only FPG was determined on reevaluation and, based on a first cutoff made after 5 years of follow-up, the authors estimated that if they had done an OGTT in this last cutoff, the incidence would have been ~30% greater (~1% annually) (31). This theoretical figure would be similar to that of our study, in which we found 10.8 new cases of diabetes/1,000 person-years. If we assume these data for the overall population of Asturias aged ≥30 years (762,822 inhabitants according to the census of 2004), we would have the alarming figure of ~7,000 new cases of type 2 diabetes every year in our community.

As in other studies (31,32), both IFG and IGT, as well as family history of diabetes, low physical activity, and core components of the metabolic syndrome such as obesity, hypertension, hypertriglyceridemia, and low HDL cholesterol, were important individual risk factors for development of diabetes in our study. Interestingly, low education level was an even stronger predictor of diabetes than other clinical or biological variables, supporting previous reports that highlight its importance in the development of diabetes (33,34).

After introducing all these variables into a multivariate model, both FPG and 2-h plasma glucose showed the strongest association with diabetes. Of the two, FPG conferred the highest risk, this being a common finding in most studies (29–31). However, it should be stressed that the diabetes risk profile can best be stratified by adding the 2-h plasma glucose measure to FPG by performing an OGTT, because their effects are cumulative. This observation is not surprising, considering that the metabolic determinants of both variables are different: having a normal FPG requires adequate basal insulin secretion and appropriate hepatic insulin sensitivity to control hepatic glucose output, whereas maintaining a normal postload glucose level after an OGTT requires an adequate β-cell secretory response as well as adequate hepatic and especially peripheral insulin sensitivity. Abnormalities of these metabolic functions characterize IFG and IGT, and the worst insulin resistance–insulin secretion patterns are seen in the IFG-IGT group (35,36). In our study, subjects with isolated IGT had a 50% lower risk than those with isolated IFG, but those with both IFG-IGT combined had a more than fivefold higher risk than those with just IFG alone. Performing an OGTT enables identification of these very high-risk persons in whom preventive measures should be intensified. It should also be remembered that 2-h plasma glucose is a better predictor of death and cardiovascular disease than is FPG (37), such that performing an OGTT would also provide a better definition of cardiovascular risk than FPG alone.

Triglycerides and BMI were also strongly predictive of diabetes, and, in addition to glucose measurements, they could be useful in defining high-risk individuals. A family history of diabetes, although one of the strongest known risk factors for development of diabetes, failed to enter the model. This variable, though, like all self-reported data could be misclassified.

In summary, this 6-year, prospective study carried out in a low-risk Spanish Caucasian population showed an incidence rate of type 2 diabetes of 10.8 cases/1,000 person-years. FPG and 2-h plasma glucose were highly predictive of diabetes, and their effects were additive. Including both glucose measurements best defined the diabetes risk in this population.

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