Differences in Cardiovascular Risk Factors, Insulin Resistance, and Insulin Secretion in Individuals With Normal Glucose Tolerance and in Subjects With Impaired Glucose Regulation

The Telde Study

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OBJECTIVE — To assess the cardiovascular risk profile, the degree of insulin resistance, and β-cell secretion in a cohort of subjects with different categories of impaired glucose regulation (IGR): impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and combined IFG/IGT.

RESEARCH DESIGN AND METHODS — We studied 902 nondiabetic subjects between 30 and 80 years of age, recruited from a cross-sectional population-based study in Telde, Gran Canaria Island, Spain. Categories of glucose tolerance were defined according to 2003 modified American Diabetes Association criteria. Risk factors for cardiovascular disease, the presence of the metabolic syndrome, and indirect measures of both insulin resistance and β-cell function were analyzed.

RESULTS — A total of 132 (14.6%) participants had isolated IFG, 59 (6.5%) isolated IGT, and 48 (5.3%) combined IFG/IGT. Groups with normal glucose tolerance (NGT) and combined IFG/IGT had, respectively, the most favorable and unfavorable levels of cardiovascular risk factors, metabolic syndrome rates, and measures of insulin resistance. Subjects with IFG and IGT showed an intermediate profile between NGT and IFG/IGT categories. We found no significant differences between IFG and IGT in cardiovascular risk factors, metabolic syndrome prevalence, or insulin resistance. The IFG group exhibited a more impaired insulin secretion than those with IGT or IFG/IGT.

CONCLUSIONS — Individuals with IGR, especially those with IFG/IGT, have increased values of cardiovascular risk factors and higher indexes of insulin resistance. Groups with isolated IFG and isolated IGT present similar cardiovascular risk profiles. Subjects with IFG are characterized by more defective β-cell function than other forms of IGR.

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Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment for insulin resistance; IFG, impaired fasting glucose; IGR, impaired glucose regulation; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; QUICKI, quantitative insulin-sensitivity check index.

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

In 1997, the American Diabetes Association (ADA) issued new diagnostic criteria for diabetes and established a new category of impaired glucose regulation (IGR) called impaired fasting glucose (IFG), a fasting category analogous to impaired glucose tolerance (IGT) and defined as a fasting plasma glucose (FPG) between 6.1 and 6.9 mmol/l (1). In 2003, based on epidemiological predictive data from different populations showing that decreasing the lower limit of IFG would optimize its sensitivity and specificity for predicting future diabetes, the ADA established a new cutoff point of 5.6 mmol/l (2).

Although both IFG and IGT are risk factors for diabetes and cardiovascular disease (CVD) (3), IGT is more consistently associated with an increase in cardiovascular-related and all-cause mortality (4–9). Moreover, evidence that interventions may reduce progression to diabetes is limited to IGT (10–12).

To explain a different prognostic value of IFG and IGT on the risk of diabetes and CVD, different studies have analyzed the prevalence of cardiovascular risk factors, insulin sensitivity, and β-cell function among subjects with different categories of IGR (13–22). However, results have been discordant, and most studies were performed before the introduction of the 2003 ADA criteria.

Here, we have compared the cardiovascular risk profile (traditional and new risk factors), the prevalence of the metabolic syndrome, as well as different indexes for the assessment of insulin-glucose homeostasis in subjects with normal glucose tolerance (NGT) and IGR that participated in the Telde Study, a population-based survey performed in Gran Canaria Island, Spain.

RESEARCH DESIGN AND METHODS

— The Telde Study is a cross-sectional population-based study

on the prevalence of diabetes and cardiovascular risk factors in Telde, a city of ~85,000 people located on the island of Gran Canaria, Spain. The Canarian population is mainly of Caucasian origin, with only minor contributions from other ethnic groups. The study population and design of this survey have been previously described (23). In summary, a stratified sample of 1,193 subjects ≥30 years of age was randomly selected from the local 1998 census. A total of 1,030 of those selected subjects gave their written informed consent for participation in the study, which was carried out according to the declaration of Helsinki and approved by the ethics committee of the Hospital Universitario Insular of Las Palmas. Participants filled out a survey questionnaire, underwent a physical examination, gave blood samples, and, except for those with diabetes, underwent a 75-g standardized oral glucose tolerance test (OGTT). Weight and height were measured without shoes and in light clothing. Waist circumference was measured midway between the iliac crest and the costal margin, and hip circumference was measured at the level of the trochanters. Blood pressure was measured twice, in the sitting position, using a manual mercury sphygmomanometer, and the mean of the two readings was used for analysis.

After exclusion of those with known or newly diagnosed diabetes, 902 subjects were included in this study and classified into categories of glucose tolerance according to current ADA criteria (1), with the 2003 modifications (2) regarding the diagnosis of IFG. We defined NGT as an FPG and 2-h plasma glucose of, respectively, <5.6 mmol/l and <7.8 mmol/l, isolated IFG as 5.6–7.0 mmol/l and <7.8 mmol/l, isolated IGT as <5.6 mmol/l and 7.8–11 mmol/l, and IFG/IGT as 5.6–7.0 mmol/l and 7.8–11 mmol/l.

For the diagnosis of metabolic syndrome, we followed the 2005 International Diabetes Federation consensus (24): waist circumference ≥94 cm in men and ≥80 cm in women plus two or more of the following components: serum triglycerides ≥1.7 mmol/l; serum HDL cholesterol <1.03 mmol/l in men and <1.29 mmol/l in women; blood pressure ≥130/85 mmHg or previously treated hypertension; and diabetes, IGT, or FPG ≥5.6 mmol/l.

Laboratory analysis

Plasma glucose, total cholesterol, HDL cholesterol, and triglycerides were determined by spectrophotometric methods and C-reactive protein and lipoprotein(a) by nephelometry, in all cases using a Dimension RxL autoanalyzer (Dade-Behring, Liederbach, Germany). LDL cholesterol was calculated by the Friedewald formula. Plasma insulin was measured by a chemiluminescent assay (Elecsys 2010; Roche Diagnostics, Basel). Whole blood was stabilized with EDTA for analysis of glycated hemoglobin (HbA_{1c} [A1C]) by high-performance liquid chromatography (HA-8140; Menarini Diagnostics-Arkray, Kyoto, Japan). Citrate-stabilized plasma was prepared for analysis of plasminogen activator inhibitor-1 (PAI-1; Imubind plasma PAI-1 enzyme-linked immunosorbent assay; American Diagnostica, Greenwich, CT), fibrinogen (modified Clauss procedure, STA fibrinogen; Diagnostica Stago, Milan, Italy), and von Willebrand factor (Vidas von Willebrand factor enzyme-linked immunosorbent assay; bioMérieux, Lyon, France). Homocysteine was measured by fluorescent inmunoanalysis (Abbott Diagnostics, Abbott Park, IL). Blood samples were placed in ice water, centrifuged, and stored frozen at −80°C until final analysis.

Insulin resistance was estimated using three indirect indexes: homeostasis model assessment for insulin resistance (HOMA-IR), according to the formula HOMA-IR = fasting insulin (mU/l) × FPG (mmol/l)/22.5 (25); quantitative insulin-sensitivity check index (QUICKI) = 1 ÷ (log fasting insulin + log fasting glucose in mg/dl) (26); and the insulin sensitivity index corrected for fat-free mass (M_{ffm}/I) described by McAuley et al. (27) as exp [2.63 − 0.28 ln (insulin in mU/l) − 0.31 ln (triglycerides in mmol/l)]. For the assessment of pancreatic β-cell function, we used the HOMA for β-cell (25) as follows: HOMA-β = 20 × fasting insulin (mU/l) ÷ fasting glucose (mmol/l) − 3.5.

Statistical analysis

For each study group related to the status of glucose tolerance, basal characteristics were analyzed as percentages and means. These were compared using the χ^2 test and *F* test, respectively. Because the average ages showed differences among the groups, we obtained the percentages and means of the markers of the cardiovascular risk adjusted by age using logistic regression and ANCOVA, respectively. When necessary, numerical variables were logarithmically transformed to reduce skewness and values expressed as geometric means. Homogeneity of groups was determined when the percentages and the means showed significant differences.

To further explore the correlation between glucose and insulin in each group, logarithm of fasting insulin concentrations was plotted against basal plasma glucose, and the following ANCOVA model was considered:

$$\mu\ (\text{log-insulin})_{i,j} = \theta + \gamma_i + \beta_i\ (\text{fasting glucose})_{i,j}$$

where i = NGT, IFG, IGT, or IFG/IGT and $\mu\ (\text{log-insulin})_{i,j}$ represents the expected log-insulin for an individual belonging to group i and with basal glucose $(\text{fasting glucose})_{i,j}$. Thus, the parameter γ_i represents the group effects ($\gamma_{NGT} = 0$ is the reference category), and the slope β_i is the variation rate for $\mu\ (\text{log-insulin})_{i,j}$ for unity of variation of the basal glucose. The model was estimated by the maximum likelihood method. In all cases, a contrast was considered statistically significant when the *P* value was ≤0.05.

RESULTS — Table 1 shows the demographic characteristics of the survey population. A total of 663 subjects (73.5%) had NGT, 132 (14.6%) had isolated IFG, 59 (6.5%) had isolated IGT, and 48 (5.3%) had combined IFG/IGT. Using the new ADA criteria, the absolute crude prevalence rates of isolated IFG and IGT (with or without IFG) in the 1,030 subjects from our whole sample were 12.8 and 10.4%, respectively. Subjects with IGT and IFG/IGT were older than those with NGT, and individuals with IGT were older than those with IFG. IFG and IFG/IGT were more prevalent in men, and IGT was more prevalent in women. People with NGT had a higher level of education than those with IGR.

Table 2 provides information on cardiovascular risk factors, insulin resistance, and β-cell function for each group. The NGT and the combined IFG/IGT groups had, respectively, the most favorable and unfavorable cardiovascular risk profiles and metabolic syndrome rates, whereas individuals with either IFG or IGT exhibited an intermediate outline. Individual risk factors for CVD were not statistically different between IFG and IGT categories.

Insulin resistance calculated by the HOMA-IR, McAuley, and QUICKI indexes (Table 2) was significantly increased in the three groups with IGR

Table 1—*Characteristics of the survey population by group*

	NGT	Isolated IFG	Isolated IGT	IFG/ IGT	*P*	Homogeneity groups
n	663	132	59	48	—	—
Age	45.1 ± 10.8	48.0 ± 10.4	53.6 ± 14.7	52.7 ± 11.0	<0.001	{1,2} {2,4} {3,4}
Sex (%)						
Men	37.9	54.5	44.1	52.1	—	—
Women	62.1	45.5	55.9	47.9	0.002	{1,3} {2,3,4}
Familial diabetes (%)	36.7	45.5	35.6	50.0	0.088	—
Smoking (%)	26.8	22.7	28.8	18.8	0.468	—
Alcohol drinking (%)						
<30 g/day	27.2	30.3	18.6	35.4	—	—
≥30 g/day	5.7	9.1	10.2	4.2	0.242	—
Education level (%)						
First grade or below	29.4	35.6	52.5	54.2	—	—
Secondary/tertiary	70.6	64.4	47.5	45.8	<0.001	{1,2} {3,4}

Data are *n*, means ± SD, or %.

versus subjects with NGT. The individuals with IFG/IGT were the most insulin resistant. There were no differences between IFG and IGT groups regarding insulin sensitivity. Compared with NGT and IFG groups, subjects identified as having IGT and IFG/IGT showed significantly greater β-cell function, as calculated by the HOMA-β index (Table 2).

For the ANCOVA model, the graphical exploration of insulin against plasma glucose concentrations showed that the correlation between glucose and insulin was positive in the NGT, isolated IGT, and combined IFG/IGT groups, whereas it tended to be negative in the IFG group. This prompted us to consider a common slope for NGT, IGT, and combined IFG/IGT groups, but different from that for the IFG group. The estimation for the common slope $\beta_{NGT} = \beta_{IGT} = \beta_{IFG/IGT} = \beta$ was 0.021 (95% CI 0.015–0.027), whereas that corresponding to the IFG group was −0.008 (−0.027 to 0.012). However, the difference of slopes $\beta - \beta_{IFG}$ (0.029 [0.008–0.049]) maintained statistical significance ($P = 0.006$).

CONCLUSIONS — Before the 2003 ADA recommendation for diagnosis of IFG, most epidemiological studies coincided to indicate that IGT was considerably more prevalent than IFG, with sex differences between the two categories (IFG was more common in men, and IGT in women) (3). However, the introduction of the new ADA diagnostic criteria has led to a notable increase in the prevalence of IFG and, consequently, the number of individuals at risk for developing diabetes (2,21,28–30). In our population, as a result of the change in criteria, we identified 100 new individuals with IFG (75% of the IFG group) and 29 with IFG/IGT (60.4% of the combined IFG/IGT group), increasing the prevalence of isolated IFG from 2.8 to 12.8%. Interestingly, 59% of subjects with IGT had FPG <5.6 mmol/l, which demonstrates that restricting the use of OGTT only to subjects with IFG is insufficient to accurately detect most cases of IGT, as was also observed in other studies (13,31).

Several studies have been performed searching for differences in CVD risk factors among IFG, IGT, and IFG/IGT subjects that could explain the increased cardiovascular risk in the IGT population (13–22). Although in some of these studies IGT was more strongly associated with hypertension, hypertriglyceridemia, and elevated levels of C-reactive protein (14,20), in general there are not substantial differences between IFG and IGT. In contrast, the combination of IFG and IGT has been consistently associated with a more adverse cardiovascular risk profile than either of the two isolated categories.

Nevertheless, most of these studies were carried out before the last ADA recommendation to lower the threshold for high fasting glucose to <5.6 mmol/l. Subjects with FPG between 5.6 and 6.1 mmol/l might reasonably display a less adverse metabolic profile, such as has been recently suggested (30), and their incorporation into the group of IFG could reduce the global cardiovascular risk for this category. In fact, using the 2003 ADA criteria, Blake et al. (21) found no differences in CVD risk factors between subjects with isolated IFG and subjects with NGT, whereas the IGT and IFG/IGT groups exhibited an elevated prevalence of cardiovascular risk factors and metabolic syndrome

Our findings do not coincide with the study by Blake et al. (21). We found significant differences between the normal population and all groups with IGR (including IFG). Furthermore, the measures of cardiovascular risk factors in the subset of individuals with IFG and FPG between 5.6 and 6.1 mmol/l were equivalent to those observed among subjects with FPG >6.1 mmol/l (data not shown). As in the earlier studies, subjects with IFG/IGT in our population also presented the most unfavorable cardiovascular risk factor profiles.

Although there is some overlap between IFG and IGT, there is evidence that both categories represent different subpopulations with different alterations in glucose homeostasis (13,32). The published studies looking at insulin resistance and β-cell function in IFG and IGT have discrepancies probably caused by ethnic differences or the different methods used to assess insulin resistance and insulin secretion. Longitudinal studies in Pima Indians using a direct measure of insulin resistance revealed that individuals with isolated IFG and isolated IGF have similar impairments of insulin action, but those with isolated IFG have a more pronounced defect in early insulin secretion and increased endogenous glucose output. Individuals with only a transient deterioration to IGT showed no decrease in early insulin secretion (13,33). Recently, Festa et al. (20), with minimal model analysis, showed similar results among the multiethnic U.S. population participating in the Insulin Resistance Atherosclerosis Study.

In contrast to the rather uniform data obtained with direct measures of insulin sensitivity, the application of surrogate markers (HOMA and insulin secretion index based on the insulin-to-glucose ratio measured during an OGTT) has provided contradictory results in IGR populations. Several authors (14,17,18) have reported increased insulin resistance in IFG, IGT, and IFG/IGT populations, and they found defective insulin release only in those with isolated IFG. By contrast, Heldgaard et al. (19) found no differences in insulin resistance or insulin secretion between IFG and IGT populations (the combined IFG/IGT group was included in the IGT group). On the other side, in the Botnia study (32) and the Risk Factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes Study (15), IGT was related to impaired insulin secretion and IFG to increased insulin resistance. In our study, we used the HOMA-IR, QUICKI, and McAuley indexes for the evaluation of insulin resistance. All three indexes have been validated using gold standard methods (27,34–36), although the McAuley index has not been previously evaluated in populations with IGR. We found that all groups with IGR were more insulin resistant than individuals with NGT. There were no significant differences between the IFG and IGT populations, and the combined IFG/IGT group had the highest level of insulin resistance. Additionally, PAI-1, a hemostatic variable probably more strongly linked to insulin resistance (37), was the only new cardiovascular risk factor that showed a statistically significant difference among groups.

With the HOMA-β, we evaluated β-cell function, which was significantly lower in IFG individuals compared with those with IGT or IFG/IGT. These findings were also supported by the results of our model to explain the correlation between glucose and insulin in each group. Although this is not a validated method to evaluate insulin resistance or β-cell function, it intuitively showed that the relationship between FPG and fasting insulin was different between IFG individuals and the other groups. The correlation between glycemia and insulinemia was positive in NGT, isolated IGT, and combined IFG/IGT groups (the higher the plasma glucose, the more elevated the insulin concentration), but it tended to be negative, albeit nonsignificantly, in the IFG group (the higher the plasma glucose, the lower was the insulin concentration). In fact, the difference between the common

Table 2—*Prevalences and means, adjusted by age, of CVD risk factors, metabolic syndrome, and insulin sensitivity and secretion indexes*

	NGT	Isolated IFG	Isolated IGT	IFG/IGT	*P*	Homogeneity groups
n	663	132	59	48	—	—
A1C (%)	4.88 (4.85–4.91)	4.99 (4.92–5.05)	4.95 (4.85–5.04)	5.29 (5.18–5.39)	<0.001	{1,3} {2,3} {4}
Hypertension (%)	30.1	34.5	39.6	55.4	<0.001	{1,2,3} {4}
Waist (cm)	93.9 (93.0–94.9)	97.6 (95.5–99.7)	99.9 (96.8–103.1)	103.1 (99.7–106.6)	<0.001	{1} {2,3} {3,4}
Waist-to-hip ratio (cm)	0.91 (0.91–0.92)	0.94 (0.93–0.96)	0.94 (0.92–0.96)	0.95 (0.93–0.98)	<0.001	{1,3} {2,3,4}
BMI (kg/m^2)	27.4 (27.0–27.7)	28.4 (27.6–29.1)	29.6 (28.4–30.8)	31.0 (29.7–32.3)	<0.001	{1,2} {2,3} {3,4}
Total cholesterol (mmol/l)	5.43 (5.36–5.50)	5.63 (5.47–5.79)	5.38 (5.24–5.62)	5.74 (5.48–6.00)	0.022	—
HDL cholesterol (mmol/l)	1.43 (1.41–1.45)	1.42 (1.37–1.48)	1.37 (1.29–1.45)	1.32 (1.23–1.41)	0.097	—
LDL cholesterol (mmol/l)	3.44 (3.38–3.50)	3.57 (3.43–3.71)	3.30 (3.09–3.51)	3.65 (3.42–3.88)	0.047	—
Triglycerides (mmol/l)*	1.10 (1.06–1.14)	1.23 (1.13–1.34)	1.41 (1.25–1.60)	1.49 (1.30–1.71)	<0.001	{1,2} {2,3,4}
Fibrinogen (mg/dl)	3.17 (3.12–3.22)	3.10 (3.00–3.21)	3.26 (3.09–3.42)	3.27 (3.09–3.45)	0.290	—
von Willebrand factor (IU/dl)	107 (104–110)	100 (94–106)	113 (104–122)	107 (97–117)	0.076	—
Homocysteine (μmol/l)	11.3 (10.9–11.8)	12.0 (11.0–12.9)	11.4 (9.9–12.8)	11.4 (9.8–12.9)	0.709	—
PAI-1 (ng/ml)	25.5 (24.2–26.8)	30.1 (27.2–33.0)	32.5 (28.1–37.0)	38.1 (33.2–43.0)	<0.001	{1} {2,3} {3,4}
C-reactive protein ≤1 (%)	96.5	95.5	98.3	97.9	0.730	—
Insulin (pmol/l)	45.8 (43.7–47.9)	56.3 (51.0–62.3)	66.8 (57.2–77.9)	76.2 (64.4–90.0)	<0.001	{1} {2,3} {3,4}
Lipoprotein(a) (mg/l)	136.9 (126.0–148.8)	135.2 (112.3–162.8)	109.7 (82.8–145.3)	158.3 (116.1–215.9)	0.353	—
Metabolic syndrome (%)	13.2	57.2	64.4	75.6	<0.001	{1} {2,3} {4}
HOMA-IR	1.31 (1.25–1.38)	1.99 (1.78–2.23)	1.88 (1.58–2.23)	2.81 (2.33–3.40)	<0.001	{1} {2,3} {4}
HOMA-β	22.24 (21.05–23.50)	22.33 (19.75–25.25)	33.08 (27.41–39.96)	31.56 (25.74–38.74)	<0.001	{1,2} {3,4}
McAuley index	8.39 (8.21–8.57)	7.66 (7.26–8.05)	7.19 (6.59–7.79)	6.56 (5.89–7.22)	<0.001	{1} {2,3} {3,4}
QUICKI	0.37 (0.37–0.38)	0.35 (0.34–0.36)	0.35 (0.34–0.36)	0.33 (0.31–0.34)	<0.001	{1} {2,3} {4}

Data are *n*, means (95% CI), or geometric means (95% CI) for variables with skewed distribution.

slope for NGT, IGT, and combined IFG/IGT and the slope corresponding to IFG was statistically significant.

The nature of our study permits us only to insinuate a pathophysiological interpretation of these results. However, because the relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose production and insulin secretion, the whole of our findings suggest that IFG subjects have elevated plasma glucose concentrations because of a defect in the basal secretion of insulin. In contrast, the predominant disturbance in other forms of IGR would be insulin insensitivity. In these cases, endogenous glucose production would be initially regulated by a compensatory increase in the secretion of basal insulin (IGT), but the plasma glucose concentration would finally become elevated as a consequence of an augment of hepatic insulin resistance and the incapacity of the β-cell to adequately increase the secretion of insulin.

In summary, this population-based survey shows that IGR individuals have a higher cardiovascular risk than the normal population. Those with IFG and IGT have similar CVD risk profiles, and combined IFG/IGT is associated with the highest cardiovascular risk profile. We found no significant differences between IFG and IGT in insulin resistance, but the IFG group exhibited a greater impairment in insulin secretion.

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