Differences in Insulin Resistance in Nondiabetic Subjects With Isolated Impaired Glucose Tolerance or Isolated Impaired Fasting Glucose

Andreas Festa,[1,2] Ralph D'Agostino, Jr.,[3] Anthony J.G. Hanley,[4] Andrew J. Karter,[5] Mohammed F. Saad,[6] and Steven M. Haffner[1]

Both impaired glucose tolerance (IGT) (as defined by the 1985 World Health Organization criteria) and impaired fasting glucose (IFG) (as defined by the 1997 American Diabetes Association criteria) represent intermediate metabolic states between normal and diabetic glucose homeostasis. Cardiovascular disease may be related to postglucose load rather than fasting glycemia, i.e., IGT rather than IFG. We hypothesized that subjects with IGT may be more insulin resistant and have higher levels of common cardiovascular risk factors than those with isolated IFG. In the Insulin Resistance Atherosclerosis Study (IRAS), we studied S_i and first-phase insulin secretion (acute insulin response [AIR]), as derived from a frequently sampled intravenous glucose tolerance test, as well as common cardiovascular risk factors in four different glucose tolerance categories (NFG/NGT [$n = 654$], NFG/IGT [$n = 255$], IFG/NGT [$n = 59$], and IFG/IGT [$n = 102$]) among nondiabetic subjects. Subjects with isolated postchallenge hyperglycemia (NFG/IGT) had lower S_i (means ± SE: 2.10 ± 0.04 vs. 2.59 ± 0.13 × 10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$; $P = 0.005$), lower proinsulin levels (34.4 ± 1.8 vs. 42.0 ± 4.5 pmol/l; $P = 0.03$), higher AIR (273.1 ± 18.1 vs. 215.9 ± 30.0 pmol/l; $P = 0.04$), higher C-reactive protein (2.49 ± 0.3 vs. 1.49 ± 0.5 mg/l; $P = 0.0015$), and higher triglyceride levels (137.7 ± 5.5 vs. 108.4 ± 8.9 mg/dl; $P = 0.0025$) than subjects with isolated fasting hyperglycemia (IFG/NGT). The relation of insulin resistance to glucose tolerance category was consistently seen in women and men and across the three ethnic groups of the IRAS (non-Hispanic whites, African Americans, and Hispanics). Nondiabetic individuals with isolated postchallenge hyperglycemia (IGT) are more insulin resistant than individuals with isolated fasting hyperglycemia (IFG). The risk factor pattern (including increased insulin resistance) seen in isolated IGT identifies a subgroup of nondiabetic individuals who are likely to benefit from early intervention. *Diabetes* 53: 1549–1555, 2004

Both impaired glucose tolerance (IGT) (as defined by the 1985 World Health Organization [WHO] criteria [1]) and impaired fasting glucose (IFG) (as defined by the 1997 American Diabetes Association [ADA] criteria [2]) represent intermediate metabolic states between normal and diabetic glucose homeostasis. There is a significant discordance in classifying individuals into these two categories (3,4). Although both categories identify individuals at risk for diabetes (3,5,6), the cardiovascular risk associated with IGT and IFG, respectively, is still a matter of debate (3,7,8); in fact, it has been suggested that cardiovascular disease (CVD) may be more strongly related to postglucose load rather than fasting glycemia (9–11), and insulin resistance may partially explain this observation. Mechanisms underlying these associations are still poorly understood. Most recently, it has been shown in the STOP-NIDDM study that treatment of postprandial hyperglycemia with acarbose resulted in improved cardiovascular outcome (12).

Differences in the risk of developing clinical events (in particular, CVD) may be explained by differences in metabolic characteristics (including insulin resistance and insulin secretion) and the cardiovascular risk factor profile between individuals with IFG and IGT, respectively (13–16). However, significant controversy still exists in the literature, in particular with respect to insulin secretion and insulin resistance (13–16). These controversial findings may be explained by different methods to assess insulin resistance; only one study used a direct measure (euglycemic clamp) (13), whereas others used an indirect measure based on fasting glucose and insulin values (homeostasis model assessment [HOMA]) (14–16).

By using a direct measure of insulin resistance (a frequently sampled intravenous glucose tolerance test [FSIGTT] with minimal model analysis), we hypothesized that subjects with isolated IGT may be more insulin resistant and have higher levels of common cardiovascular risk factors than subjects with isolated IFG, and we tested this hypothesis in the nondiabetic population of the Insulin

From the [1]Department of Medicine, University of Texas Health Science Center, San Antonio, Texas; [2]Eli Lilly and Company, Area Medical Center, Vienna, Austria; the [3]Department of Public Health Sciences, Wake Forest University School of Medicine, Winston Salem, North Carolina; the [4]Department of Medicine, Mount Sinai Hospital, University of Toronto, Ontario, Canada; the [5]Kaiser Research Center, Northern California, Oakland, California; and the [6]Department of Medicine, UCLA School of Medicine, Los Angeles, California.

Address correspondence and reprint requests to Steven M. Haffner, Department of Medicine, University of Texas Health Science Center, 7703 Floyd Curl Dr., MC 7873, San Antonio, TX 78229-3900. E-mail: haffner@uthscsa.edu.

Received for publication 28 October 2003 and accepted in revised form 15 March 2004.

ADA, American Diabetes Association; AIR, acute insulin response; CRP, C-reactive protein; CVD, cardiovascular disease; FSIGTT, frequently sampled intravenous glucose tolerance test; HOMA, homeostasis model assessment; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; IRAS, Insulin Resistance Atherosclerosis Study; PAI-1, plasminogen activator inhibitor-1; PI/I ratio, proinsulin-to-insulin ratio; WHO, World Health Organization.

Resistance Atherosclerosis Study (IRAS), a large tri-ethnic population. S_i and first-phase insulin secretion (acute insulin response [AIR]) were assessed by FSIGTT, HOMA was calculated as described (17), and, along with traditional cardiovascular risk factors, fasting proinsulin levels and the proinsulin-to-insulin (PI/I) ratio were assessed as surrogate markers of cardiovascular risk as well as insulin action and insulin secretion.

RESEARCH DESIGN AND METHODS

The IRAS is a multicenter epidemiological study aimed at exploring relationships between insulin resistance, cardiovascular risk factors, and disease across different ethnic groups and varying states of glucose tolerance. A full description of the design and methods of the IRAS has been published previously (18). The IRAS protocol was approved by local institutional review committees, and all subjects gave informed consent.

A total of 1,624 individuals participated in the IRAS. Of those, 1,070 were nondiabetic, as defined by WHO (1) and ADA (2) criteria (fasting and 2-h glucose concentrations <7.0 and <11.1 mmol/l, respectively). For the purpose of this report, glucose tolerance status was defined based on a standard 75-g oral glucose tolerance test using both fasting (ADA, 1997) and 2-h postchallenge (WHO, 1985) glucose concentrations. IFG was defined as fasting glucose concentrations between 6.1 and 7.0 mmol/l (ADA), and IGT was defined as a 2-h postchallenge glucose between 7.8 and 11.1 mmol/l (WHO). This stratification yielded four different nondiabetic subgroups: NFG/NGT (normal fasting and postchallenge glucose tolerance, $n = 654$; fasting and 2-h glucose concentrations <6.1 and <7.8 mmol/l, respectively), NFG/IGT (isolated postchallenge hyperglycemia, $n = 255$; fasting glucose <6.1 mmol/l and 2-h glucose between 7.8 and 11.1 mmol/l), IFG/NGT (isolated fasting hyperglycemia, $n = 59$; fasting glucose between 6.1 and 7.0 mmol/l and 2-h glucose <7.8 mmol/l), and IFG/IGT (combined fasting and postchallenge hyperglycemia, $n = 102$; fasting glucose between 6.1 and 7.0 mmol/l and 2-h glucose between 7.8 and 11.1 mmol/l).

Smoking status was recorded as "none," "past," or "current" using a standard questionnaire. Race and ethnicity were assessed by self-report. Blood pressure was measured using standard methods, and hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication.

Assessment of glucose tolerance and insulin sensitivity. A standard 75-g oral glucose tolerance test was performed, and an FSIGTT (19) with minimal-model analysis (20) was performed to assess insulin sensitivity. Two modifications of the original protocol were used. An injection of regular insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance. In addition, the reduced sampling protocol (which required 12 rather than 30 plasma samples) was used because of the large number of subjects. Insulin sensitivity, expressed as the insulin sensitivity index (S_i), was calculated by mathematical modeling methods (MINMOD, version 3.0 [1994]). AIR was calculated as the mean of 2- and 4- min insulin concentrations after glucose administration.

Height, weight, girth measurements, and laboratory measurements were performed using standard methods, as described previously (21). Insulin was measured using the dextran-charcoal radioimmunoassay, which cross-reacts with proinsulin, fasting serum intact proinsulin, and 32-33 split proinsulin. These proinsulins were determined by means of highly specific two-site monoclonal antibody–based immunoradiometric assays (coefficient of variation [CV] 14% for proinsulin and 18% for 32-33 split proinsulin) (22). Intact proinsulin and 32-33 split proinsulin were determined at the laboratory of the Department of Clinical Biochemistry at Addenbrook's Hospital, Cambridge, U.K. (C.N. Hales). Inflammatory proteins (C-reactive protein [CRP], plasminogen activator inhibitor-1 [PAI-1], and fibrinogen) were measured at the Laboratory for Clinical Biochemistry Research, University of Vermont (R.P. Tracy), as described (21). CRP was measured by in-house ultrasensitive competitive immunoassay (antibodies and antigens from Calbiochem, La Jolla, CA) with an interassay CV of 8.9%, fibrinogen was measured in citrated plasma with a modified clot-rate assay using the Diagnostica STAGO ST4 instrument (CV 3.0%), and PAI-1 was also measured in citrated plasma using a two-site immunoassay that is sensitive to free PAI-1 but not to PAI-1 complexed with tissue plasminogen activator (CV 14%).

Statistical analysis. Clinical and metabolic data were displayed using means and SEs for continuous variables and counts and percentages for categorical variables. Unadjusted comparisons were made among the four groups defined by fasting and 2-h glucose tolerance status using ANOVA techniques with pairwise comparisons made using t tests (Table 1). Next, a series of linear models were fit using ANCOVA techniques. Outcome variables were log transformed for analyses when necessary to satisfy the normality assumption in the models, and back-transformed values are shown (Table 2, Fig. 1). First, models were fit to examine the impact of glucose tolerance category on the outcomes adjusting for demographic characteristics: age, sex, clinical center, ethnicity, and smoking. To further explore the impact of metabolic covariates on the differences in variables of interest among the groups, four additional models were fit, each including the demographic characteristics and one additional variable: BMI, waist circumference, insulin resistance (S_i), or AIR. These metabolic covariates have been related to the variables of interest in previous analyses. Finally, a full model was fit adjusting for demographic characteristics plus the four additional variables described above. To account for baseline differences in age, sex, and ethnicity among the different glucose tolerance categories, stratified analyses were performed as well as analyses examining whether there were interactions among the glucose tolerance category variable and sex, ethnicity, and age.

All analyses were conducted using the Statistical Analysis System (SAS, version 8.02; SAS Institute, Cary NC). P values <0.05 (two sided) were considered statistically significant.

RESULTS

Data in nondiabetic subjects according to fasting and 2-h postchallenge glucose tolerance category. Significant differences between the four groups were seen with respect to sex (higher prevalence of isolated postchallenge hyperglycemia [NFG/IGT] in women, higher prevalence of isolated fasting hyperglycemia [IFG/NGT] in men), ethnicity, and hypertension (Table 1). An overall comparison of continuous variables yielded P values of <0.0001 for all variables, as shown on Table 2, except for total cholesterol ($P = 0.11$), LDL cholesterol ($P = 0.21$), HDL cholesterol ($P = 0.04$), LDL size ($P = 0.01$), diastolic blood pressure ($P < 0.01$), and the PI/I ratio ($P = 0.0005$).

The NFG/NGT group (group 1; normal glucose tolerance) had the lowest levels of cardiovascular risk factors (differences versus the combined IFG/IGT intolerance group [group 4] in all listed variables, except total cholesterol, LDL cholesterol, and LDL size; differences versus isolated IGT [group 2] in all listed variables except LDL cholesterol, HDL cholesterol, and diastolic blood pressure; and differences versus isolated IFG (group 3) in all listed variables except BMI, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, LDL size, CRP, and fibrinogen). Note that for several cardiovascular risk factors (namely BMI, triglycerides, total cholesterol, LDL size, CRP, and fibrinogen), isolated IGT (group 2) had an unfavorable risk factor profile versus the normal group (NFG/NGT), whereas these variables were not different between NFG/NGT and isolated IFG (group 3). Vice versa, only diastolic blood pressure was higher in IFG versus NFG/NGT (but not in IGT vs. NFG/NGT).

The IFG/IGT group (combined fasting and postchallenge hyperglycemia; group 4) had the highest levels of cardiovascular risk factors (differences versus IGT [group 2] in all glucose metabolism variables, except 2-h insulin, PI/I ratio, and S_i, and differences in PAI-1; differences versus IFG [group 3] in all glucose metabolism variables except fasting glucose, proinsulin, PI/I ratio, and AIR, and differences in CRP). These findings indicate a graded risk across the glucose tolerance categories, ranging from the lowest risk in NFG/NGT to the highest risk in IFG/IGT (combined defect), with an intermediate risk for the two groups presenting with isolated (fasting or postchallenge) hyperglycemia.

Isolated postchallenge hyperglycemia (NFG/IGT) versus isolated fasting hyperglycemia (IFG/NGT).

TABLE 1
Characteristics of nondiabetic subjects according to fasting and 2-h glucose tolerance status

	NFG/NGT[1]	NFG/IGT[2]	IFG/NGT[3]	IFG/IGT[4]	*P* 1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Clinical and metabolic data										
n	654	255	59	102	—	—	—	—	—	—
Sex (%, M/F)	44/56	37/63	64/36	41/59	—	—	—	—	—	—
Ethnicity (%) (NHW, AA, HIS)	40/26/34	42/21/37	46/27/27	31/41/27	—	—	—	—	—	—
Hypertension (yes/no)	25/75	41/59	44/56	43/57	—	—	—	—	—	—
Smoking (never/past/current)	45/39/16	46/38/16	42/39/19	48/36/16	—	—	—	—	—	—
Age (years)	53.7 ± 0.3	57.0 ± 0.5	56.7 ± 1.1	55.9 ± 0.8	<0.0001	0.007	0.013	0.8	0.3	0.5
BMI (kg/m^2)	27.3 ± 0.2	29.3 ± 0.3	28.6 ± 0.7	33.4 ± 0.5	<0.0001	0.08	<0.0001	0.4	<0.0001	<0.0001
Waist (cm)	87.6 ± 0.5	92.8 ± 0.8	93.1 ± 1.6	101.0 ± 1.2	<0.0001	0.001	<0.0001	0.8	<0.0001	<0.0001
Fasting glucose (mg/dl)	93.6 ± 0.3	98.8 ± 0.4	114.9 ± 0.9	116.0 ± 0.7	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.4
2-h glucose (mg/dl)	104.5 ± 0.8	161.9 ± 1.2	113.6 ± 2.6	168.1 ± 2.0	<0.0001	0.0007	<0.0001	<0.0001	0.0079	<0.0001
Fasting insulin (pmol/l)	67.4 ± 1.9	84.4 ± 3.9	91.9 ± 8.9	118.5 ± 9.3	<0.0001	0.0002	<0.0001	0.3	<0.0001	0.01
2-h insulin (pmol/l)	336.5 ± 14.1	645.8 ± 40.4	444.4 ± 71.1	677.6 ± 71.0	<0.0001	<0.01	<0.0001	0.001	0.6	0.001
Proinsulin/intact (pmol/l)	23.7 ± 0.7	34.4 ± 1.8	42.0 ± 4.5	49.2 ± 4.0	<0.0001	<0.0001	<0.0001	0.03	<0.0001	0.13
Proinsulin/split (pmol/l)	9.3 ± 1.2	11.9 ± 3.0	13.4 ± 8.3	67.1 ± 6.9	<0.0001	<0.0001	<0.0001	0.03	<0.0001	0.2
PI/I ratio	0.35 ± 0.01	0.40 ± 0.02	0.45 ± 0.05	0.42 ± 0.03	0.003	0.004	0.015	0.2	0.7	0.4
$S_i \times 10^{-4}$ ($min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	3.19 ± 0.05	2.10 ± 0.04	2.59 ± 0.13	1.94 ± 0.06	<0.0001	0.003	<0.0001	0.005	0.2	0.0008
AIR (pmol/l)	333.9 ± 13.2	273.1 ± 18.1	215.9 ± 30.0	208.4 ± 22.9	0.0007	<0.0001	<0.0001	0.04	0.004	0.8
HOMA-IR	56.6 ± 2.7	75.6 ± 4.3	96.4 ± 8.9	132.7 ± 6.8	0.0002	<0.0001	<0.0001	0.036	<0.0001	0.0012
Cardiovascular risk data										
n	654	255	59	102						
Triglycerides (mg/dl)	104.4 ± 2.6	137.7 ± 5.5	108.4 ± 8.9	131.8 ± 8.2	<0.0001	0.6	<0.0001	0.0025	0.5	0.029
Cholesterol (mg/dl)	209.7 ± 1.6	216.9 ± 2.6	208.7 ± 5.4	214.2 ± 4.1	0.021	0.9	0.3	0.17	0.6	0.4
LDL cholesterol (mg/dl)	139.8 ± 1.4	143.0 ± 2.2	142.1 ± 4.5	147.1 ± 3.5	0.2	0.6	0.053	0.9	0.3	0.4
HDL cholesterol (mg/dl)	48.0 ± 0.6	46.3 ± 0.9	45.0 ± 2.0	44.2 ± 1.5	0.13	0.14	0.016	0.5	0.2	0.7
LDL size (Å)	261.5 ± 0.4	259.1 ± 0.6	260.6 ± 1.3	260.8 ± 1.0	0.0011	0.5	0.5	0.3	0.15	0.9
Systolic blood pressure (mmHg)	118.3 ± 0.6	124.0 ± 1.0	127.1 ± 2.1	126.8 ± 1.6	<0.0001	<0.0001	<0.0001	0.18	0.13	0.9
Diastolic blood pressure (mmHg)	76.7 ± 0.3	77.8 ± 0.5	79.7 ± 1.1	78.7 ± 0.8	0.09	0.0091	0.024	0.11	0.3	0.5
CRP (mg/l)	1.50 ± 0.1	2.49 ± 0.3	1.49 ± 0.5	3.08 ± 0.7	<0.0001	0.9	<0.0001	0.0015	0.11	<0.0001
Fibrinogen (mg/dl)	265.8 ± 2.2	281.6 ± 3.8	268.8 ± 7.4	286.4 ± 6.1	0.0002	0.7	0.0008	0.13	0.5	0.06
PAI-1 (ng/ml)	13.9 ± 0.6	18.6 ± 1.3	19.4 ± 2.8	24.2 ± 2.6	<0.0001	0.003	<0.0001	0.7	0.007	0.10

Data are means ± SE. Unadjusted *P* values are for overall comparisons for categorical variables (χ^2) and for pairwise comparisons for continuous variables (ANOVA). AA, African Americans; NHW, non-Hispanic whites; HIS, Hispanics.

TABLE 2
S_i ($\times 10^{-4}$ min^{-1} · μU^{-1} · ml^{-1}), AIR (pmol/l), proinsulin (pmol/l), triglycerides (mg/dl), and CRP (mg/l) in nondiabetic subjects with isolated postchallenge hyperglycemia (NFG/IGT) versus isolated fasting hyperglycemia (IFG/NGT)

	NFG/IGT	IFG/NGT	*P*
S_i			
Demo plus BMI	2.22 ± 0.05	2.69 ± 0.12	0.004
Demo plus waist	2.32 ± 0.05	2.71 ± 0.12	0.013
Demo plus S_i	—	—	—
Demo plus AIR	2.13 ± 0.04	2.50 ± 0.11	0.017
Full model	—	—	—
AIR			
Demo plus BMI	261.9 ± 16.9	216.1 ± 27.7	0.07
Demo plus waist	251.7 ± 16.0	213.2 ± 26.9	0.12
Demo plus S_i	241.8 ± 15.3	209.3 ± 25.7	0.16
Demo plus AIR	—	—	—
Full model	—	—	—
Proinsulin			
Demo plus BMI	33.4 ± 1.7	39.5 ± 4.0	0.047
Demo plus waist	31.7 ± 1.6	38.7 ± 3.8	0.014
Demo plus S_i	31.4 ± 1.7	38.9 ± 4.1	0.013
Demo plus AIR	34.8 ± 1.9	42.2 ± 4.5	0.030
Full model	31.2 ± 1.6	39.5 ± 3.8	0.003
Triglycerides			
Demo plus BMI	135.2 ± 5.4	106.8 ± 8.3	0.0017
Demo plus waist	132.5 ± 5.3	105.7 ± 8.2	0.0025
Demo plus S_i	130.7 ± 5.6	105.6 ± 8.5	0.0058
Demo plus AIR	137.5 ± 5.8	108.9 ± 8.9	0.0030
Full model	128.7 ± 5.6	105.1 ± 8.5	0.0088
CRP			
Demo plus BMI	2.14 ± 0.2	1.59 ± 0.5	0.041
Demo plus waist	1.99 ± 0.2	1.55 ± 0.5	0.083
Demo plus S_i	1.97 ± 0.2	1.55 ± 0.5	0.12
Demo plus AIR	2.29 ± 0.3	1.75 ± 0.5	0.09
Full model	1.94 ± 0.2	1.55 ± 0.4	0.12

Data are means ± SE. Demo, adjusted for age, sex, clinical center, ethnicity, and smoking; full model, adjusted for all covariates listed.

Table 1 shows unadjusted data, Fig. 1 shows demographically adjusted data, and Table 2 shows data for selected variables of interest (S_i, AIR, proinsulin, triglycerides, and CRP) adjusted for a number of covariates, including demographic covariates (age, sex, ethnic group, clinical center, and smoking), BMI, waist, S_i, and AIR.

In unadjusted analyses (Table 1), as expected, individuals with isolated IGT (group 2 vs. group 3) had higher levels of 2-h glucose and lower levels of fasting glucose. Moreover, these individuals had higher levels of 2-h insulin, AIR, and triglycerides and lower levels of intact and split proinsulin, as well as lower S_i, and lower HOMA of insulin resistance (IR) (HOMA-IR) than individuals with isolated IFG (group 3). Of note, differences for the latter two indicators of insulin sensitivity pointed in different directions; the S_i value suggested greater insulin resistance among individuals with isolated postchallenge hyperglycemia (IGT), whereas the HOMA-IR indicated greater relative insulin resistance in the group with isolated IFG.

Differences in S_i between the two groups were only slightly attenuated after adjusting for BMI, waist, or AIR (Table 2, AIR). Differences in HOMA were unaffected by adjustments for these covariates (data not shown). Also, differences in levels of proinsulin and triglycerides remained significant after adjusting for demographic and metabolic covariates (Table 2, proinsulin and triglycerides), whereas differences in CRP levels were no longer significant after adjusting for waist, S_i, or AIR (Table 2, CRP).

Stratified analyses by ethnicity. Stratified analyses indicated consistency of results. Differences were seen in all subgroups, which were comparable to results found in the overall population, reaching statistical significance for some but not all comparisons (data not shown). No significant interactions were detected when analyzing the effect of ethnicity on the differences of S_i, HOMA-IR, AIR, proinsulin, triglycerides, and CRP among the four groups (demographically adjusted interaction terms $P = 0.6$, 0.08, 0.8, 0.4, 0.3, and 0.17, respectively).

Stratified analyses by sex. Stratified analyses indicated consistency of results. Differences were seen in all subgroups, which were comparable to results found in the overall population, reaching statistical significance for some but not all comparisons (data not shown). No significant interactions were detected when analyzing the effect of sex on the differences of S_i, HOMA-IR, AIR, proinsulin, triglycerides, and CRP among the four groups (demographically adjusted interaction terms $P = 0.8$, 0.4, 0.17, 0.8, 0.8, and 0.5, respectively).

Stratified analyses by age. No significant interactions were detected when analyzing the effect of age on the differences of S_i, HOMA-IR, AIR, proinsulin, triglycerides, and CRP among the four groups (demographically adjusted interaction terms $P = 0.14$, 0.2, 0.3, 0.2, 0.2, and 0.3, respectively).

DISCUSSION

We have shown in a large tri-ethnic population that nondiabetic individuals characterized by isolated postchallenge hyperglycemia (IGT) are more insulin resistant (as directly measured) than individuals with isolated fasting hyperglycemia (IFG). Also, isolated IGT was related to increased AIR, higher triglyceride and CRP levels, and lower proinsulin levels than isolated IFG. The current study is unique for its large sample size, its tri-ethnic composition, and the direct assessment of insulin resistance.

Our findings support previous reports indicating that these two categories of impaired glucose metabolism represent two metabolically distinct entities. This refers to both *1*) measures of glucose/insulin metabolism and *2*) common cardiovascular risk factors.

Glucose/insulin metabolism. Based on the results of the present study, we conclude that individuals with isolated IGT are more insulin resistant than those with isolated IFG. The difference in insulin resistance was slightly attenuated after adjusting for waist (but less so for BMI), even though both measures of body fat were not different between the two groups. Assuming that waist circumference (rather than BMI) reflects abdominal/visceral adiposity, our findings indicate that higher insulin resistance in isolated IGT may be partially explained by increased abdominal/visceral obesity in these individuals. Also, adjusting for AIR slightly attenuated the differences, suggesting that differences in S_i between the two groups may be due to differences in β-cell function. In fact, AIR, reflecting first-phase insulin secretion, was lower in IFG versus IGT, suggesting a defect in first-phase insulin secretion (in IFG, AIR was as low as in individuals with a combined IFG/IGT

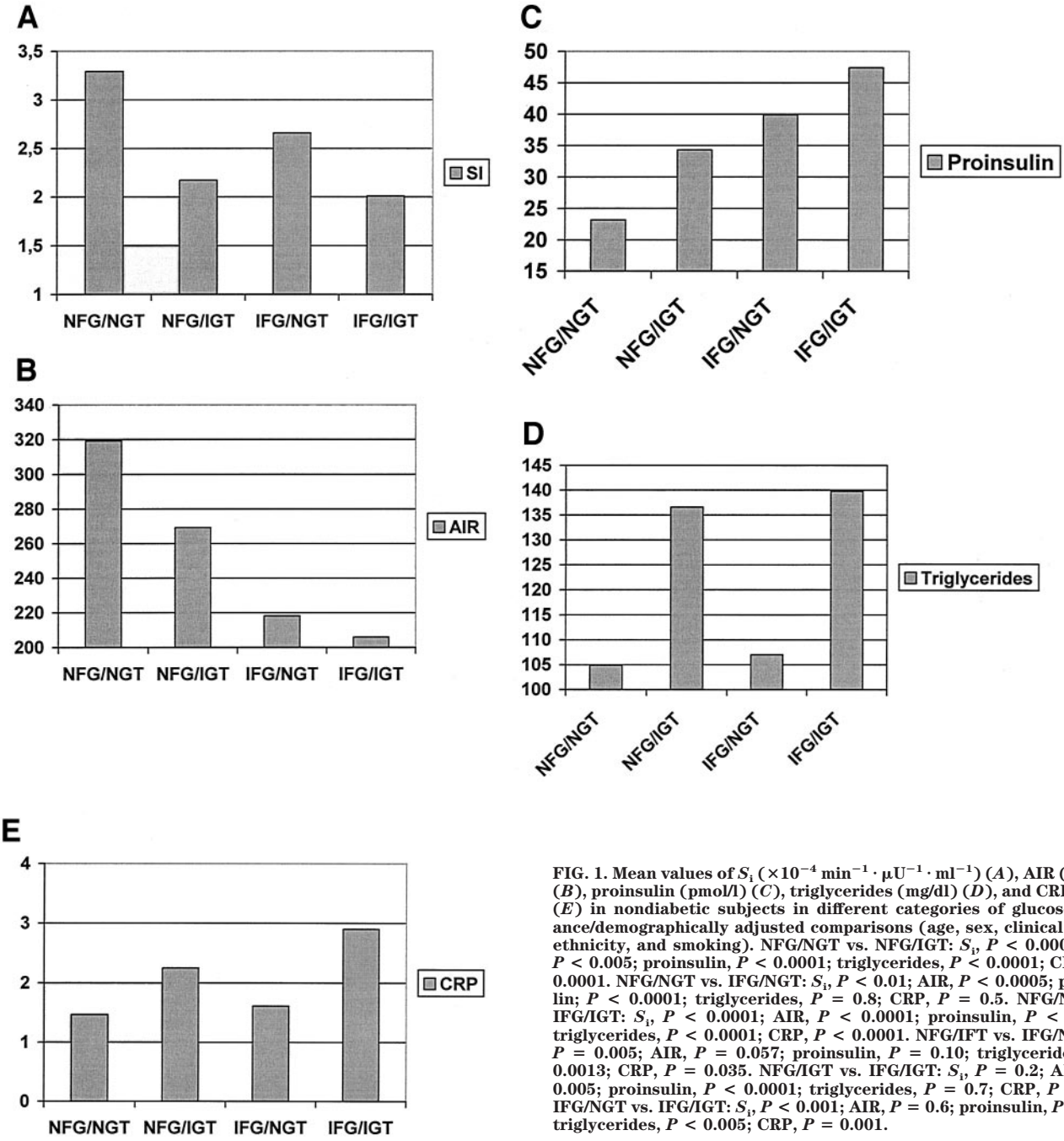

FIG. 1. Mean values of S_i ($\times 10^{-4}$ min^{-1} · μU^{-1} · ml^{-1}) (*A*), AIR (pmol/l) (*B*), proinsulin (pmol/l) (*C*), triglycerides (mg/dl) (*D*), and CRP (mg/l) (*E*) in nondiabetic subjects in different categories of glucose tolerance/demographically adjusted comparisons (age, sex, clinical center, ethnicity, and smoking). NFG/NGT vs. NFG/IGT: S_i, $P < 0.0001$; AIR, $P < 0.005$; proinsulin, $P < 0.0001$; triglycerides, $P < 0.0001$; CRP, $P < 0.0001$. NFG/NGT vs. IFG/NGT: S_i, $P < 0.01$; AIR, $P < 0.0005$; proinsulin; $P < 0.0001$; triglycerides, $P = 0.8$; CRP, $P = 0.5$. NFG/NGT vs. IFG/IGT: S_i, $P < 0.0001$; AIR, $P < 0.0001$; proinsulin, $P < 0.0001$; triglycerides, $P < 0.0001$; CRP, $P < 0.0001$. NFG/IFT vs. IFG/NGT: S_i, $P = 0.005$; AIR, $P = 0.057$; proinsulin, $P = 0.10$; triglycerides, $P = 0.0013$; CRP, $P = 0.035$. NFG/IGT vs. IFG/IGT: S_i, $P = 0.2$; AIR, $P < 0.005$; proinsulin, $P < 0.0001$; triglycerides, $P = 0.7$; CRP, $P < 0.05$. IFG/NGT vs. IFG/IGT: S_i, $P < 0.001$; AIR, $P = 0.6$; proinsulin, $P = 0.10$; triglycerides, $P < 0.005$; CRP, $P = 0.001$.

disturbance; Fig. 1). These findings suggest that postchallenge (and potentially postprandial) hyperglycemia is the result of increased insulin resistance rather than impaired insulin secretion, whereas fasting hyperglycemia reflects defective β-cell function.

Fasting proinsulin levels were higher in IFG versus IGT. This finding is difficult to interpret, because a higher PI/I ratio (which is not different between isolated IGT and isolated IFG in the present study) has been related to decreased AIR and has therefore (rather than higher fasting proinsulin levels) been suggested as a marker of impaired β-cell function in nondiabetic (23) and newly diagnosed type 2 diabetic individuals (24).

Previous studies investigating insulin resistance and insulin secretion in populations with IGT and IFG have yielded conflicting results (13–16). Studies using HOMA as a marker of insulin resistance have shown that individuals with IFG have increased insulin resistance (14,16) or impaired insulin secretion rather than increased insulin resistance (15). These inconsistencies are not unexpected given that HOMA bases assessments of insulin sensitivity strictly on fasting insulin and glucose measures, whereas MINMOD S_i and the hyperinsulinemic clamp use a whole time series of measures from preload and postload. Using equations based on fasting glucose levels is misleading, because fasting glucose levels determine the category into which an individual falls; individuals with isolated IFG have, by definition, higher fasting glucose levels than individuals with isolated IGT. We therefore suggest that, although quite adequate in other contexts, the HOMA

model provides an inadequate assessment of insulin sensitivity when comparing isolated IGT and IFG.

IGT was related to impaired insulin secretion in the Botnia study (14) and the Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study (16), whereas IGT was related to features of the insulin resistance syndrome in a general population (15). Only one previous study used a direct measure of insulin resistance (hyperinsulinemic euglycemic clamp) (13). Findings from this study in Pima Indians are in agreement with results of the current study, showing that individuals with IFG or IGT, compared to individuals with normal fasting glucose/normal glucose tolerance (NFG/NGT), had increased insulin resistance as well as impaired insulin secretion, the latter being more pronounced in individuals with IFG (13). This consistency in findings from S_i and clamp studies is not unexpected given that the clamp shares MINMOD S_i assessments based on a time series of metabolic measures rather than relying on fasting measures (such as HOMA).

Based on these previous reports and the results of the present study, it is likely that the seemingly discrepant findings are in fact the result of different methods that have been used to assess insulin resistance and insulin secretion.

Cardiovascular risk factors. No differences in major metabolic cardiovascular risk factors (total, LDL, and HDL cholesterol, blood pressure) were detected between individuals with isolated IGT versus individuals with isolated IFG. However, individuals with isolated IGT (versus isolated IFG) had higher insulin resistance and higher triglyceride and CRP levels, which was considered to indicate higher cardiovascular risk (25–27). On the other hand, individuals with isolated IFG (versus isolated IGT) had higher HOMA values and higher proinsulin levels, both of which have also been related to an increased risk of CVD (28,29). However, taking into account the problems with construct validity introduced when using HOMA-IR in this context (as discussed above) and the relative scarcity of data on the relation of proinsulin levels to cardiovascular risk, a greater cardiovascular risk for individuals with isolated IGT seems to emerge. The relation of IFG and IGT, respectively, to cardiovascular risk factors and CVD is still a matter of debate (3,8). In a previous report, free fatty acid levels were lower (both vs. NGT and vs. IGT) and proinsulin levels tended to be higher (significant vs. NGT; NS vs. IGT) in isolated IFG (16). In contrast, in a female population with previous gestational diabetes, common cardiovascular risk factors were higher in IFG (vs. NGT; vs. IGT for BMI and waist only) (30). Few outcome data are currently available, suggesting that IGT (rather than IFG) is related to carotid intima-media thickness, a surrogate marker of CVD, or is related to CVD itself (8). Finally, we have also shown that individuals with a combined IFG/IGT disturbance present with the most unfavorable cardiovascular risk factor profile. This is in agreement with findings from the Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study, showing the highest intima-media thickness levels in the combined IFG/IGT group (6).

We would also like to mention weaknesses and specific strengths of this report. The present study reports data from cross-sectional analyses; therefore, no conclusions regarding cause-effect relationships can be made. On the other hand, this is the first study analyzing insulin resistance, as directly measured, in a large tri-ethnic population within subgroups of nondiabetic individuals with different metabolic states. The fact that the main finding of this study (increased insulin resistance in isolated IGT) was seen in all three ethnic groups, and among women and men, strengthens the significance and the generalizability of the study.

The present study may be clinically relevant; first, because it identifies a subgroup among nondiabetic (and potentially "pre-diabetic") individuals that may benefit from insulin-sensitizing interventions, and second, because the same group of individuals may be exposed to an increased cardiovascular risk and may therefore be targets for (early) CVD prevention. Further studies are underway to determine the risk of incident diabetes in the nondiabetic IRAS population according to different glucose tolerance categories.

In summary, we have shown that individuals with isolated IGT are more insulin resistant than individuals with isolated IFG. This finding, along with differences in common cardiovascular risk factors, may explain the increased cardiovascular risk associated with IGT (rather than IFG), as seen in some studies, such as the DECODE study (11). The risk factor pattern (including increased insulin resistance) seen in isolated IGT identifies a subgroup of nondiabetic individuals that is likely to benefit from early intervention.

ACKNOWLEDGMENTS

This work was supported by the National Heart, Lung and Blood Institute (grants Hl47887, Hl47889, Hl47890, Hl47892, Hl47902, Hl55208, and R01 Hl58329) and the General Clinic Research Centers Program (grants NCRR GCRC, M01 RR431, and M01 RR01346).

REFERENCES

1. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Organization, 1985 (Tech. Rep. Ser., no. 727)
2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
3. Unwin N, Shaw J, Zimmet P, Alberti KGMM: Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 19:708–723, 2002
4. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and World Health Organization diagnostic criteria. *Diabetes Care* 20:1859–1862, 1997
5. Alberti KGMM: The clinical implications of impaired glucose tolerance. *Diabet Med* 13:927–937, 1996
6. Shaw JE, Zimmet PZ, De Courten M, Dowse GK, Chitson P, Gareeboo H, Hemraj F, Fareed D, Tuomilehto J, Alberti KGMM: Impaired fasting glucose or impaired glucose tolerance: what best predicts future diabetes in Mauritius? *Diabetes Care* 22:399–402, 1999
7. Hanefeld M, Schaper F, Henkel E, Siegert G, Koehler C, Temelkova-Kurktschiev T: Impaired fasting glucose is not a risk factor for atherosclerosis. *Diabet Med* 16:212–218, 1999
8. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. *Diabetes Care* 22:920–924, 1999
9. Haffner SM: The importance of hyperglycemia in the nonfasting state to the development of cardiovascular disease. *Endocr Rev* 19:583–592, 1998
10. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege

E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360–367, 1998
11. The DECODE Study Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999
12. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. *JAMA* 290:486–494, 2003
13. Weyer C, Bogardus C, Pratley RE: Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 48:2197–2203, 1999
14. Tripathy D, Carlsson M, Almgren P, Isomaa B, Taskinen M-R, Tuomi T, Groop LC: Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. *Diabetes* 49:975–980, 2000
15. Davies MJ, Raymond NT, Day JL, Hales CN, Burden AC: Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. *Diabet Med* 17:433–440, 2000
16. Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F, Temelkova-Kurktschiev T: Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 26:868–874, 2003
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in men. *Diabetologia* 28:412–419, 1985
18. Wagenknecht LE, Mayer EJ, Rewers M, Haffner SM, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF, Bergman RN, Hamman R: The Insulin Resistance Atherosclerosis Study (IRAS): objectives, design and recruitment results. *Ann Epidemiol* 5:464–471, 1995
19. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. *Endocr Rev* 6:45–86, 1985
20. Pacini G, Bergman RN: MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. *Comput Methods Programs Biomed* 23:113–122, 1986
21. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM: Elevated levels of acute phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes* 51:1131–1137, 2002
22. Festa A, D'Agostino R Jr, Mykkänen L, Tracy RP, Zaccaro DJ, Hales CN, Haffner SM: Relative contribution of insulin and its precursors to fibrinogen and PAI-1 in a large population with different states of glucose tolerance: the Insulin Resistance Atherosclerosis Study (IRAS). *Arterioscler Thromb Vasc Biol* 19:562–568, 1999
23. Mykkänen L, Haffner SM, Hales CN, Rönnemaa T, Laakso M: The relation of proinsulin, insulin, and proinsulin-to-insulin ratio to insulin sensitivity and acute insulin response in normoglycemic subjects. *Diabetes* 46:1990–1995, 1997
24. Mykkänen L, Zaccaro DJ, Hales CN, Festa A, Haffner SM: The relation of proinsulin and insulin to insulin sensitivity and acute insulin response in subjects with newly diagnosed type II diabetes. *Diabetologia* 42:1060–1066, 1999
25. Howard G, O'Leary DH, Zaccaro D, Haffner SM, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R: Insulin sensitivity and atherosclerosis: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 93:1809–1817, 1996
26. Castelli WP, Anderson K, Wilson PW, Levy D: Lipids and risk of coronary heart disease: the Framingham Study. *Ann Epidemiol* 2:23–28, 1992
27. Blake GJ, Ridker PM: Novel clinical markers of vascular wall inflammation. *Circ Res* 89:763–771, 2001
28. Hanley AJG, Williams K, Stern MP, Haffner SM: Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease. *Diabetes Care* 25:1177–1184, 2002
29. Yudkin JS, May M, Elwood P, Yarnell JWG, Greenwood R, Davey Smith G: Concentrations of proinsulin like molecules predict coronary heart disease risk independently of insulin: prospective data from the Caerphilly Study. *Diabetologia* 45:327–336, 2002
30. Pallardo LF, Herranz L, Martin-Vaquero PM, Garcia-Ingelmo T, Grande C, Janez M: Impaired fasting glucose and impaired glucose tolerance in women with prior gestational diabetes are associated with a different cardiovascular profile. *Diabetes Care* 26:2318–2322, 2003