Prevalence of Insulin Resistance in Metabolic Disorders

The Bruneck Study

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The prevalence of insulin resistance in the most common metabolic disorders is still an undefined issue. We assessed the prevalence rates of insulin resistance in subjects with impaired glucose tolerance (IGT), NIDDM, dyslipidemia, hyperuricemia, and hypertension as identified within the frame of the Bruneck Study. The study comprised an age- and sex-stratified random sample of the general population (n = 888; aged 40–79 years). Insulin resistance was estimated by homeostasis model assessment ($HOMA_{IR}$), preliminarily validated against a euglycemic-hyperinsulinemic clamp in 85 subjects. The lower limit of the top quintile of $HOMA_{IR}$ distribution (i.e., 2.77) in nonobese subjects with no metabolic disorders (n = 225) was chosen as the threshold for insulin resistance. The prevalence of insulin resistance was 65.9% in IGT subjects, 83.9% in NIDDM subjects, 53.5% in hypercholesterolemia subjects, 84.2% in hypertriglyceridemia subjects, 88.1% in subjects with low HDL cholesterol, 62.8% in hyperuricemia subjects, and 58.0% in hypertension subjects. The prevalence of insulin resistance in subjects with the combination of glucose intolerance (IGT or NIDDM), dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia and/or low HDL cholesterol), hyperuricemia, and hypertension (n = 21) was 95.2%. In isolated hypercholesterolemia, hypertension, or hyperuricemia, prevalence rates of insulin resistance were not higher than that in nonobese normal subjects. An appreciable number of subjects (n = 85, 9.6% of the whole population) was insulin resistant but free of IGT, NIDDM, dyslipidemia, hyperuricemia, and hypertension. These results from a population-based study documented that *1*) in hypertriglyceridemia and a low HDL cholesterol state, insulin resistance is as common as in NIDDM, whereas it is less frequent in hypercholesterolemia, hyperuricemia, and hypertension; *2*) the vast majority of subjects with multiple metabolic disorders are insulin resistant; *3*) in isolated hypercholesterolemia, hyperuricemia, or hypertension, insulin resistance is not more frequent than can be expected by chance alone; and *4*) in the general population, insulin resistance can be found even in the absence of any major metabolic disorders. *Diabetes* 47:1643–1649, 1998

Insulin resistance is thought to be a common finding in several metabolic disorders, including glucose intolerance, dyslipidemia, hyperuricemia, and hypertension. This concept has emerged mainly from case-control studies (1–6) and so far has not been substantiated by large population-based surveys. In fact, the few studies carried out in epidemiological settings have focused on impaired glucose tolerance (IGT) or NIDDM only (1,7). As a consequence, our knowledge about the prevalence of insulin resistance in the most common metabolic disorders is still insufficient.

The accurate and precise assessment of insulin sensitivity in an individual is based on the use of the glucose clamp technique (9), which is unanimously considered the gold standard (10). Alternative methods have been proposed and used, but they have several limitations. When glucose clamp was used as the reference standard, the variance in insulin sensitivity explained by these alternative methods was ~65% with the short insulin-tolerance test (11) and 30–50% with the frequently sampled, intravenous glucose tolerance test analyzed with the minimal model (12,13). Even these alternative methods, for their complexity and/or high cost, are unsuitable for epidemiological studies.

Over the last two decades, fasting serum insulin has been used as a surrogate index of insulin sensitivity in several epidemiological studies (14–18), assuming that hyperinsulinemia is a proxy of insulin resistance. However, fasting insulin cannot explain >30–40% of the variance in glucose clamp–determined insulin sensitivity (19). A better, although still inaccurate, approach to estimating insulin sensitivity (or insulin resistance) is the homeostasis model assessment (HOMA), developed by Matthews et al. (20) with computer-aided modeling of fasting glucose and insulin concentrations. These authors reported that HOMA-based insulin resistance scores strongly correlate with glucose clamp–assessed insulin sensitivity (20). However, validation was carried out in only a few subjects, and the glucose clamp studies were not performed in conjunction with glucose tracer infusion, so that it was impossible to precisely quantitate overall glucose disposal.

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GIR, glucose infusion rate; HOMA, homeostasis model assessment; $HOMA_{IR}$, HOMA of insulin resistance; IGT, impaired glucose tolerance.

Indeed, endogenous glucose production is not always completely suppressed by physiological hyperinsulinemia, especially in diabetic subjects (2), and the measurement of glucose infused to maintain euglycemia during glucose clamp can substantially underestimate the exact rate of glucose disposal.

In the present study, we estimated insulin sensitivity by HOMA in subjects of the Bruneck Study, a population-based survey on atherosclerosis and its risk factors. Our goal was to evaluate the prevalence of insulin resistance in the most common metabolic disorders: IGT, NIDDM, dyslipidemia, hyperuricemia, and hypertension. In this study we arbitrarily included essential hypertension among metabolic disorders for ease of presentation and in keeping with the concept that hypertension has a metabolic component (21).

Before using the HOMA as an estimate of insulin sensitivity, we validated it with the euglycemic-hyperinsulinemic clamp combined with tritiated glucose infusion—the gold standard measure of insulin sensitivity—in a group of 85 subjects, half of whom had NIDDM.

RESEARCH DESIGN AND METHODS

Validation of HOMA

Subjects. This study included 85 subjects (43 men, 42 women) aged 47.7 ± 1.4 years (mean ± SE) with an average BMI of 28.0 ± 0.5 kg/m^2. Of these subjects, 41 were NIDDM patients who were recruited among those regularly attending the Diabetes Clinic of the University of Verona and who were willing to participate in the study. In these subjects (34 men, 7 women), the mean age was 56.4 ± 0.9 years, the BMI was 26.5 ± 0.4 kg/m^2, and fasting glucose was 10.2 ± 0.3 mmol/l. Diabetes was treated with diet only in 8 patients and with oral agents in 33 patients (13 with sulfonylureas, 20 with sulfonylureas + biguanides). Patients who were on insulin treatment were excluded. Nondiabetic subjects (n = 44) were recruited by an advertisement. These subjects (9 men, 35 women) had an average age of 39.0 ± 1.5 years and an average BMI of 29.5 ± 1.0 kg/m^2. All participants underwent physical examination and routine blood chemistry evaluation. None of them had a history of recent acute illness or clinical evidence suggestive of cardiovascular, kidney, liver, or endocrine diseases. Body composition was measured by bioimpedance analysis (22). All subjects gave their written informed consent to participate in the study. The protocol was approved by the Ethical Committee of the Azienda Ospedaliera di Verona.

Glucose clamp. The study consisted of a 4-h euglycemic-hyperinsulinemic clamp, as originally described by De Fronzo et al. (9), associated with D-[3-^{3}H]glucose infusion, as previously reported in detail (23). Briefly, Teflon cannulas were inserted into an antecubital vein for infusion of insulin, glucose (20% dextrose), and D-[3-^{3}H]glucose, and into a contralateral heated (60°C) hand vein for arterialized blood sampling. After baseline blood collections for glucose and insulin determinations, a prime-constant (20 mU · min^{-1} · m^{-2} body surface area) insulin infusion was started and continued for 240 min. The prime dose consisted of two subsequent 5-min periods of insulin infusion at the rate of 80 and 40 mU · min · m^{-2}, respectively. Plasma glucose was clamped at ~5 mmol/l by a variable glucose infusion. In diabetic subjects, plasma glucose was left to drop until euglycemia was reached (generally within 120 min), and then was maintained at that level. A prime-constant infusion of D-[3-^{3}H]glucose was initiated at the rate of 0.45 µCi/min 2 h after the beginning of the insulin clamp and continued until the end of the study. The prime dose of labeled glucose was calculated by dividing the glucose pool (plasma glucose concentration × glucose distribution volume [assumed to be 25% of body weight]) by the product of 1.1 and glucose infusion rate (GIR) in the 100–120 min period of the clamp and then multiplying the result by the tracer infusion rate. The GIR was multiplied by 1.1 to take into account the expected 10% average increase in GIR from 100–120 min to 180–240 min of glucose clamp. As previously reported (23), with this methodological approach a steady state of tritiated glucose specific activity is obtained at 180–240 min. During this period, blood was withdrawn every 10 min to measure plasma levels of glucose, insulin, and tritiated glucose specific activity. Insulin-mediated total glucose disposal rate (TGD) was calculated by dividing the D-[3-^{3}H]glucose infusion rate by the steady state D-[3-^{3}H]glucose specific activity. More details have been reported elsewhere (23).

Analytical determinations. Plasma glucose was measured by the glucose-oxidase method on a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Serum insulin was measured by a double-antibody radioimmunoassay (24). Plasma D-[3-^{3}H]glucose specific activity was determined as described in detail elsewhere (23).

HOMA of insulin resistance. The estimate of insulin resistance by HOMA ($HOMA_{IR}$) was calculated with the formula fasting serum insulin (µU/ml) × fasting plasma glucose (mmol/l)/22.5, as described by Matthews et al. (20).

Statistical analysis. $HOMA_{IR}$ values and values of TGD during insulin clamp were $\log_e$-transformed to approximate a normal distribution. Pearson and Spearman rank correlations between $HOMA_{IR}$ and clamp-assessed insulin sensitivity were computed to validate the use of $HOMA_{IR}$ as an index of insulin sensitivity.

Insulin resistance in metabolic disorders

Subjects. The Bruneck Study is a cross-sectional, prospective population-based survey on atherosclerosis and its risk factors carried out in Bruneck, a small town of about 13,500 people in northeastern Italy. As previously reported (25,26), the baseline evaluation was carried out between July and November 1990 on subjects aged 40–79 years. Of the 4,793 subjects of the appropriate age range, 125 men and 125 women for each age decade (40–49, 50–59, 60–69, and 70–79 years) were randomly selected and invited to participate in the study. In particular, consecutive numbers were assigned to all residents of Bruneck aged 40–79 years according to alphabetical order and after sex and age-decade stratification. Then, 125 numbers each from the pool of men and women of each age-decade were blindly drawn. Of the corresponding 1,000 subjects, 936 volunteered after the purposes and modalities of the study had been carefully presented. Of those 936, 2 subjects who were insulin-treated, 17 subjects with incomplete data collection, and 29 subjects with no serum available for the measurement of insulin were excluded, which left 888 subjects (450 men, 438 women) for the current analysis.

Clinical data. The following demographic and clinical data were collected with a standardized questionnaire: sex, age, cigarette smoking, alcohol consumption, physical activity, socioeconomic status, health condition, and drug consumption. In each subject the following information about cigarette smoking was recorded: smoking status (nonsmoker, former smoker, or current smoker), average number of cigarettes smoked per day, number of years of smoking, and pack-years (i.e., number of cigarettes/day × years of smoking). Alcohol consumption was quantified by asking type and average amount of alcoholic beverages ingested daily, categorized in four categories: 0, 1–50, 51–99, and ≥100 g/day. The level of physical activity during the leisure time was defined using a three-category scale: 1 = no exercise at all; 2 = regular physical activity for up to 2 h/week (e.g., jogging, biking, swimming, playing tennis, heavy gardening); 3 = regular physical activity for >2 h/week. Socioeconomic status was defined with a two-category scale (1 = low, 2 = high) based on information about the occupational status of the person with the highest income in the household and the educational level of the proband. A high social status was assumed if the proband had ≥12 years of education and/or the occupation of the subject or his/her spouse was among those with an average monthly income of $2,000 or greater in the study area.

Physical examination data. Weight (to the nearest 0.5 kg) and height (to the nearest 0.5 cm) were measured while the subjects were fasting overnight and wearing only underwear. BMI was calculated as weight (kg) divided by height (m)^2. Subjects with BMI >25 kg/m^2 were categorized as overweight (27); this category included obese individuals (BMI >30 kg/m^2).

Blood pressure was measured with a standard mercury sphygmomanometer on the left arm after at least 10 min of rest. Mean values were determined from two independent measurements.

Laboratory data. In the morning, after an overnight fast, venous blood was sampled for the measurement of plasma concentrations of glucose and serum concentrations of total and HDL cholesterol, triglycerides, urate, and insulin. A 75-g oral glucose load was administered to all subjects but known diabetic patients to establish their glucose tolerance (normal, impaired, or diabetic). During such test, blood was withdrawn at 120 min. Plasma glucose was measured within a few hours after collection by a glucose-oxidase method. Serum total cholesterol, HDL cholesterol, triglycerides, and urate were assessed on frozen serum by standard enzymatic methods. Serum insulin was measured on sera stored at –30°C within 6 months after collection, according to the method of Hales and Randle (24). Intra- and interassay coefficients of variation were 3.2 and 6.9%, respectively.

Diagnostic criteria of metabolic diseases. NIDDM was diagnosed if a subject was taking oral hypoglycemic agents or when the subject's plasma glucose was >7.8 mmol/l at fasting and/or >11.1 mmol/l 2 h after oral glucose load (28). IGT was diagnosed when plasma glucose 2 h after oral glucose loading was 7.8–11.1 mmol/l (28). Hypercholesterolemia was established when serum cholesterol was >6.2 mmol/l (29) and hypertriglyceridemia when serum triglycerides were >2.85 mmol/l (30). Low HDL cholesterol was defined by a value <1.0 mmol/l in women and <0.9 mmol/l in men (29). Hyperuricemia was established when serum urate was >416 µmol/l in men and >387 µmol/l in women (31). Hypertension was diagnosed when systolic blood pressure was ≥160 mmHg or diastolic blood pressure was ≥95 mmHg or when an antihypertensive treatment was in progress (32).

Coexistence of all metabolic abnormalities—glucose intolerance (IGT or NIDDM) + dyslipidemia (high total cholesterol and/or high triglycerides and/or low HDL cholesterol) + hyperuricemia + hypertension—in the single individual was

TABLE 1
Main clinical features of the Bruneck Study population

	Mean or median*	SD or interquartile range*	Range
Age (years)	59	11	40–79
BMI (kg/m^2)	25	4	16–47
Total cholesterol (mmol/l)	5.74	1.03	3.07–11.35
LDL cholesterol (mmol/l)	3.51	1.00	0.64–9.36
HDL cholesterol (mmol/l)	1.45	0.36	0.69–2.97
Triglycerides (mmol/l)	1.25*	0.92–1.82*	0.43–11.22
Urate (µmol/l)	322	87	65–630
Fasting glucose (mmol/l)	5.60	1.05	3.72–14.77
Fasting insulin (pmol/l)	77*	50–116*	14–430
$HOMA_{IR}$	2.51*	1.63–3.97*	0.19–36.4
Systolic blood pressure (mmHg)	146	22	91–230
Diastolic blood pressure (mmHg)	89	10	53–126

*Median and interquartile range were used for skewed variables. n = 888: 450 men, 438 women.

arbitrarily defined as "plurimetabolic syndrome." Metabolic disorders were considered "isolated" when they were not associated with other metabolic abnormalities or excess weight (BMI >25).

Definition of insulin resistance. In each subject, the degree of insulin resistance ($HOMA_{IR}$) was computed as previously described. As extensively discussed by Matthews et al. (20), who developed the HOMA, low $HOMA_{IR}$ values indicate a high insulin sensitivity, whereas high $HOMA_{IR}$ values indicate a low insulin sensitivity (insulin resistance). In this study, the presence of insulin resistance was arbitrarily established when the proband had an $HOMA_{IR}$ value equal to or higher than the lower limit of the top quintile of $HOMA_{IR}$ distribution values (i.e., 2.77) in normal subjects (i.e., those with BMI ≤25 kg/m^2 and with no metabolic disorders). In these subjects (n = 225), the limits of $HOMA_{IR}$ values of the five quintiles were as follows: 0.19–1.11, 1.12–1.54, 1.55–2.03, 2.04–2.76, and 2.77–36.4.

Statistical analysis. Statistical analysis was performed with the SPSS 7.5 software (SPSS, Chicago). The χ^2 analysis with Yates' correction for continuity was used to compare prevalence rates of metabolic disorders across categories of insulin resistance and prevalence rates of insulin resistance in subjects with an increasing number of metabolic disorders (zero to four). In addition, we fitted logistic regression models of each metabolic disorder on quintiles of insulin resistance and potential confounders (sex, age, BMI, physical activity, smoking, alcohol consumption, and socioeconomic status). Categories of insulin resistance were modeled either as a set of indicator variables or as a set of trends (orthogonal polynomials). These multivariate analyses demonstrated that insulin resistance is an independent predictor of most metabolic disorders, and suggested an excellent fit for linear-type associations.

TABLE 2
Prevalence of metabolic diseases in the Bruneck Study population

All cases	
IGT	85 (9.6)
NIDDM	62 (7.0)
Hypercholesterolemia	256 (28.8)
Hypertriglyceridemia	76 (8.6)
Low HDL cholesterol	42 (4.7)
Hyperuricemia	137 (15.4)
Hypertension	331 (37.3)
Plurimetabolic syndrome	21 (2.4)
No metabolic abnormalities*	321 (36.1)
Isolated metabolic disorders†	
IGT	12 (1.3)
NIDDM	5 (0.6)
Hypercholesterolemia	77 (8.7)
Hypertriglyceridemia	1 (0.1)
Low HDL cholesterol	2 (0.2)
Hyperuricemia	13 (1.5)
Hypertension	44 (4.9)

Data are n (%). n = 888. *None of the above metabolic disorders; †no associated metabolic abnormalities or excess weight.

RESULTS

Validation of HOMA. Pearson's correlation between insulin sensitivity as measured by insulin clamp ("true insulin sensitivity") and as estimated by HOMA was 0.792 ($P < 0.0001$). Thus the explained variance of true insulin sensitivity by HOMA was ~65%. The strength of the correlation was almost identical in nondiabetic and diabetic subjects when the two groups were analyzed separately (r = 0.726 in nondiabetic and 0.720 in diabetic subjects). Linear regression analyses yielded similar slopes (–1.07 vs. –1.16) and intercepts (4.25 vs. 5.05) in the two groups. In the whole sample, Spearman's rank correlation was even stronger (r_s = 0.813, $P < 0.0001$).

Insulin resistance in metabolic disorders. Table 1 displays the main clinical features of subjects examined within the frame of the Bruneck Study. As reported in Table 2, the prevalence of IGT was 9.6% and that of NIDDM was 7.0%. Hypercholesterolemia was found in 28.8%, hypertriglyceridemia in 8.6%, and low HDL cholesterol in 4.7% of subjects. The prevalence of hyperuricemia was 15.4% and that of hypertension was 37.3%. The prevalence of plurimetabolic syndrome was 2.4%, about 1,000 times higher than expected if these metabolic diseases associate only by chance. It is interesting to note that the prevalence rates of these disorders in the isolated form were much lower than the overall prevalence rates (Table 2). In particular, hypertriglyceridemia and low HDL cholesterol almost never occurred as isolated disorders in the general population. About one-half of the sample (n = 474, 53.4%) consisted of normal-weight subjects (BMI ≤25), and the other half consisted of overweight individuals (n = 414, 46.6%). Of the former, 225 subjects (47.5%) had no metabolic disorders, whereas of the latter, only 95 subjects (22.9%) were free of metabolic disorders.

Table 3 shows the prevalence rates of selected metabolic disorders in the categories of insulin sensitivity (resistance) as defined by the limits of $HOMA_{IR}$ quintiles in normal-weight healthy subjects. The frequency of all metabolic disorders increased across $HOMA_{IR}$ quintiles (P < 0.05–0.001). This was true for the univariate and, in most instances, the multivariate analyses (i.e., after adjustment for sex, age, BMI, physical activity, alcohol intake, smoking, and socioeconomic status). Similar data were found after stratification by gender (male/female), BMI (normal weight/overweight), and age (40–59/60–79 years) (data not shown).

Prevalence rates of insulin resistance in selected metabolic disorders are summarized in Table 4. As expected, NIDDM, hypertriglyceridemia, and low HDL cholesterol were accompanied by insulin resistance more frequently than hypercholesterolemia, hyperuricemia, and hypertension. In the first group of conditions, the prevalence of insulin resistance was ~85%, whereas in the second group the prevalence of insulin resistance varied from ~30 to ~60%.

Table 4 also reports the prevalence rates of insulin resistance in isolated metabolic disorders (e.g., NIDDM without excess weight, dyslipidemia, hypertension, or hyperuricemia). In some cases (hypertriglyceridemia, low HDL cholesterol), the rates were too low for a meaningful interpretation. The preva-

TABLE 3
Prevalence rates (%) of metabolic disorders in categories of insulin sensitivity (resistance) as defined by the limits of $HOMA_{IR}$ quintiles in 225 normal-weight healthy subjects from the Bruneck Study

		$HOMA_{IR}$ limits						
	n	I (0.19–1.11)	II (1.12–1.54)	III (1.55–2.03)	IV (2.04–2.76)	V (2.77–36.4)	P value*	P value†
IGT	85	7.5 (8)	5.2 (5)	4.7 (6)	6.1 (10)	14.3 (56)	<0.001	0.022 (0.011)
NIDDM	62	1.9 (2)	2.1 (2)	3.1 (4)	1.2 (2)	13.3 (52)	<0.001	<0.001 (<0.001)
Hypercholesterolemia	256	19.8 (21)	16.5 (16)	28.7 (37)	27.4 (45)	34.9 (137)	<0.05	<0.001 (<0.001)
Hypertriglyceridemia	76	2.8 (5)	3.1 (3)	2.3 (3)	1.8 (3)	16.3 (64)	<0.001	<0.001 (<0.001)
Low HDL cholesterol	42	0 (0)	1.0 (1)	0.8 (1)	1.8 (3)	9.4 (37)	<0.001	0.012 (0.049)
Hyperuricemia	137	10.4 (11)	9.3 (9)	10.1 (13)	11.8 (18)	21.9 (86)	<0.001	0.005 (<0.001)
Hypertension	331	26.4 (28)	18.6 (18)	27.9 (36)	34.8 (57)	49.0 (192)	<0.001	0.018 (0.002)
Plurimetabolic syndrome	21	0 (0)	0 (0)	0.8 (1)	0 (0)	5.1 (20)	<0.001	NA (NA)

Data are prevalence rates (n). *Univariate P values for differences in prevalence rates across quintiles assessed by χ^2 test. †P values after adjusting for sex, age, BMI, physical activity, smoking, alcohol, and socioeconomic status. P values in parentheses are P values for a linear trend. These probability values were derived from logistic regression analyses of the metabolic disease on $HOMA_{IR}$ quintiles and the above covariates. NA, analysis not applicable for low numerosity in relation to the number of covariates.

lence of insulin resistance in isolated glucose intolerance (IGT + NIDDM), hypercholesterolemia, hyperuricemia, or hypertension, however, was substantially and significantly lower than in combined metabolic disorders (P < 0.05–0.01). Furthermore, when we compared the prevalence rates of insulin resistance in isolated disorders with those found in normal-weight subjects with no metabolic disorders (45 of 225 [20%]), we observed that hypercholesterolemia, hyperuricemia, and hypertension had prevalence rates of insulin resistance not significantly higher than those expected by chance.

TABLE 4
Prevalence rates (%) of insulin resistance in selected metabolic disorders

	All cases	Isolated disorders	Combined disorders
IGT	65.9 (55.6–76.2) (56/85)	33.3 (4/12)	71.2† (52/73)
NIDDM	83.9 (74.6–93.2) (52/62)	60.0 (3/5)	85.9* (49/57)
Hypercholesterolemia	53.5 (47.3–59.7) (137/256)	33.8 (26/77)	62.0† (111/179)
Hypertriglyceridemia	84.2 (75.8–92.6) (64/76)	100 (1/1)	84.0‡ (63/75)
Low HDL cholesterol	88.1 (78.1–98.1) (37/42)	50.0 (1/2)	90.0‡ (36/40)
Hyperuricemia	62.8 (54.5–71.1) (86/137)	23.1 (3/13)	66.9† (83/124)
Hypertension	58.0 (52.6–63.4) (192/331)	29.5 (13/44)	62.4† (179/287)
Plurimetabolic syndrome	95.2 (85.9–100) (20/21)	NA	NA

Data are prevalence rates (95% CI) (number of observed cases/total). *P < 0.05, †P < 0.01 for differences in prevalence of insulin resistance in isolated and combined metabolic disorders (χ^2 test); ‡analysis not applicable for low numerosity.

Coexistence of four metabolic disorders—glucose intolerance, dyslipidemia, hyperuricemia, and hypertension—in a single individual, a clinical condition we termed "plurimetabolic syndrome," was associated with a very high prevalence of insulin resistance, ~95% (Table 4). Insulin resistance had a frequency proportional (P < 0.001) to the number of metabolic abnormalities clustering within the same individual. This was observed in both men and women, in younger and older subjects, and in normal-weight and overweight individuals (Table 5).

$HOMA_{IR}$ values for 85 subjects (45 normal weight and 40 overweight) were in the top quintile of the distribution (i.e., ≥2.77), but these subjects were free of any metabolic disorders. For these subjects, we might use the term "isolated insulin resistance." This condition had a prevalence of 9.6% in the whole study population (85 of 888). When excess weight was not associated with any metabolic disorder (isolated overweight, n = 95), insulin resistance was found in 42% of cases (40 of 95).

DISCUSSION

These results from a population-based study indicated that insulin resistance is very common among subjects with metabolic diseases, although its prevalence varies substantially among clinical conditions. Higher rates of insulin resistance were found with NIDDM and hypertriglyceridemia and in the low–HDL cholesterol state (~85% of subjects), whereas lower prevalence rates were found with hypercholesterolemia, hyperuricemia, and hypertension (30–60% of subjects).

Insulin resistance seemed to be less frequent with IGT than with NIDDM. Because IGT precedes NIDDM and a decline in insulin secretion rather than an increase in insulin resistance is thought to be the event moving an individual from IGT to NIDDM (33), this result was surprising at first glance. However, the higher prevalence of insulin resistance in NIDDM might be explained by the so-called glucose toxicity (34). On the other hand, the prevalence rate of insulin resistance in NIDDM that we observed was similar to that

TABLE 5
Prevalence of insulin resistance (%) dependent on the number of metabolic disorders (0–4) occurring in the single individual

		Number of metabolic disorders				
	n	0	1	2	3	4
All	888	27	43	59	80	95
Men	450	25	39	48	77	84
Women	438	29	48	73	83	100
Age ≤60	486	30	47	70	83	100
Age >60	402	19	39	52	79	95
BMI ≤25	474	20	33	45	50	95
BMI >25	414	43	54	71	91	100

Metabolic disorders could be glucose intolerance (IGT or NIDDM), dyslipidemia (high cholesterol and/or high triglycerides and/or low HDL cholesterol), hyperuricemia, and/or hypertension. *P* value for differences in prevalence rates across categories of metabolic disorders was assessed by χ^2 test and was always <0.001.

recently reported by the investigators of the Insulin Resistance Atherosclerosis Study (7).

Hypertriglyceridemia and low HDL cholesterol almost never occurred as isolated disorders, and were nearly always associated with insulin resistance. This finding was in agreement with evidence that insulin can positively affect VLDL and HDL metabolism (35,36), so that in conditions of impaired insulin action, VLDL and HDL metabolism is altered (4,5). Hypercholesterolemia's occurrence as an isolated disorder was not accompanied by insulin resistance more frequently than expected. This result was consistent with data previously reported. Indeed, both Ferrannini and Laakso and their coworkers (37,38) did not find significant differences in insulin sensitivity in hypercholesterolemic versus normocholesterolemic subjects undergoing an insulin clamp.

The prevalence of insulin resistance in hypertension that we found in the present study (~30% of cases with isolated hypertension) was quite similar to that recently reported by Lind et al. (8), who used the insulin clamp in a case-control study. The stronger associations between insulin resistance and hypertension suggested by earlier studies (3) were probably due to selection bias related to small numbers of subjects examined. Interestingly, the prevalence we found in isolated hypertension was not significantly different from that expected by chance alone. Thus isolated hypertension does not seem to be an insulin-resistant state.

So far only few reports have focused on the relationship between insulin resistance and hyperuricemia (6,39–41), and no information is presently available on the prevalence of insulin resistance in this metabolic condition. Our data suggest that hyperuricemia is often accompanied by insulin resistance when it is associated with other metabolic disorders, but it is not an insulin-resistant state itself.

The results of our study indicate that insulin resistance is almost ubiquitous when several metabolic disorders cluster within the same individual, whereas it is rarer and often not more frequent than expected by chance when the various metabolic disorders are isolated. This finding, which was independent of gender, age, and BMI, supports the idea that insulin resistance might be a common denominator, with a pathogenic effect, in several metabolic disorders, as originally hypothesized by Reaven (42).

Among overweight subjects with no metabolic disorders, ~40% were insulin resistant. This result is consistent with recent data obtained by the European Group for the Study of Insulin Resistance, which found that ~20% of overweight but otherwise healthy subjects showed insulin resistance values in the range corresponding to the top decile of insulin-resistance distribution values in normal-weight, healthy subjects (43).

An interesting finding of our study was that a significant proportion (9.6%) of the general population aged 40–79 years was insulin resistant, even in the absence of any major metabolic disorder. In particular, 5.1% of the general population (45 of 888) consisted of normal-weight subjects who had no metabolic disorders but did show insulin resistance ($HOMA_{IR}$ >2.77). These subjects might eventually develop one or more metabolic disorders (16), and might also carry an increased cardiovascular risk (44,45). However, this hypothesis needs to be confirmed in prospective studies presently under way.

The overall prevalence of insulin resistance in the whole sample was ~45%. This result underscores the extent of the phenomenon within the general population, and indicates the large proportion of the population that might be the target of preventive measures, especially if data from preliminary reports suggesting that insulin resistance is an independent cardiovascular risk factor are confirmed.

The method we used to evaluate insulin sensitivity is not a measure of the amount of glucose metabolized per unit of body weight or lean body mass during a predetermined whole body exposure to insulin, as during the glucose clamp. However, the HOMA did allow us to rank individuals according to insulin sensitivity in a way similar to the glucose clamp. In fact, in a large number of individuals, we found a strong correlation between insulin sensitivity values generated by the two tests. In this regard, the HOMA seems to be a predictor of true insulin sensitivity comparable with the intravenous glucose tolerance test (IVGTT) combined with the minimal model, a method used largely as an alternative to the glucose clamp (7,44,46). Indeed, the correlation coefficient between insulin sensitivity measures achieved with the glucose clamp and the IVGTT/minimal model ranged from 0.30 to 0.89 (12,13,47,48), whereas the correlation between clamp and HOMA was ~0.80. Unquestionably, HOMA is less accurate and precise than the glucose clamp in measuring insulin sensitivity, but this limitation is mitigated when the number of subjects examined is large, as in our study. In addition, our results were strengthened by the fact that our study was population based, which should have minimized possible selection biases.

It could be argued that the use of sulfonylureas in subjects with diabetes might significantly affect the estimate of insulin resistance by HOMA, as these drugs are known to decrease fasting plasma glucose without substantially changing fasting plasma insulin (49). However, in our validation studies of HOMA, the correlation of insulin sensitivity estimated by such method and that measured by the glucose clamp was not substantially different in diet-treated (r = –0.87) and sulfonylurea-treated (r = –0.65) NIDDM subjects.

A possible limitation of our study was that we used an insulin assay with a potential cross-reactivity with proinsulin and split proinsulin products. This could have made the estimate of insulin sensitivity by HOMA in subjects with a remarkable amount of proinsulin, such as NIDDM patients, less accurate (50). However, the similar relationship between HOMA-determined insulin sensitivity and clamp-determined insulin sensitivity that we found in nondiabetic and diabetic subjects seems to rebut this hypothesis. In addition, raised proinsulin levels seem to be a marker of insulin resistance in nondiabetic subjects (51).

These results from a population-based study documented that *1*) with hypertriglyceridemia and a low–HDL cholesterol state, insulin resistance is as common as in NIDDM, but is less frequent with hypercholesterolemia, hyperuricemia, and hypertension; *2*) the vast majority of subjects with multiple metabolic disorders are insulin resistant; *3*) in isolated hypercholesterolemia, hyperuricemia, or hypertension, insulin resistance is not more frequent than expected by chance alone; and *4*) in the general population, insulin resistance can be found even in the absence of any major metabolic disorders. Studies carried out in different populations are needed to support and definitively qualify these conclusions.

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REFERENCES

1. Lillioja S, Mott DM, Howard BV, Bennett PH, Yki-Järvinen H, Freymond D, Nyomba BL, Zurlo F, Swinburn B, Bogardus C: Impaired glucose tolerance as a disorder of insulin action: longitudinal and cross-sectional studies in Pima Indians. *N Engl J Med* 318:1217–1225, 1988
2. DeFronzo RA: The triumvirate β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–687, 1988
3. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S: Insulin resistance in essential hypertension. *N Engl J Med* 317:350–357, 1987
4. McKane WR, Stevens AB, Woods R, Andrews WJ, Henry RW, Bell PM: The assessment of hepatic and peripheral insulin sensitivity in hypertriglyceridemia. *Metabolism* 12:1240–1245, 1990
5. Karhapaa P, Malkki M, Laakso M: Isolated low HDL cholesterol: an insulin resistance state. *Diabetes* 43:411–417, 1994
6. Vuorinen-Markkola H, Yki-Järvinen H: Hyperuricemia and insulin resistance. *J Clin Endocrinol Metab* 78:25–29, 1994
7. Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, Rewers M, Mykkanen L, Karter AJ, Hamman R, Saad MF: Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. *Diabetes* 46:63–69, 1997
8. Lind L, Berne C, Lithell H: Prevalence of insulin resistance in essential hypertension. *J Hypertens* 13:1457–1462, 1995
9. DeFronzo RA, Tobin JD, Andres R: The glucose clamp technique: a method for the quantification of beta cell sensitivity to glucose and of tissue sensitivity to insulin. *Am J Physiol* 237:E214–E223, 1979
10. Fulcher GR, Walker M, Alberti KGMM: The assessment of insulin action in vivo. In *International Textbook of Diabetes Mellitus*. Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, Eds. New York, Wiley, 1992, p. 513–530
11. Bonora E, Moghetti P, Zancanaro C, Cigolini M, Querena M, Cacciatori V, Corgnati A, Muggeo M: Estimates of in vivo insulin action in man: comparison of insulin tolerance tests and euglycemic and hyperglycemic glucose clamp studies. *J Clin Endocrinol Metab* 68:374–378, 1989
12. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YDI, Sands RE, Pei D, Savage PJ, Bergman RN, for the Insulin Resistance Atherosclerosis Study: A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. *Diabetes* 43:1114–1121, 1994
13. Saad MF, Steil GM, Kades WW, Ayad MF, Elsewafy WA, Boyadjian R, Jinagouda SD, Bergman RN: Differences between the tolbutamide-boosted and the insulin-modified minimal model protocols. *Diabetes* 46:1167–1171, 1997
14. Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passeri M, Reaven G: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 320:703–706, 1989
15. Modan M, Halkin H, Almong S, Lusky A, Eshkol A, Shefi M, Shitrit A, Fuchs Z: Hyperinsulinemia: a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 75:809–817, 1985
16. Fontbonne A, Charles MA, Thibult N, Richard JL, Claude JR, Warnet JM, Rosselin GE, Eschwege E: Hyperinsulinemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15-years follow-up. *Diabetologia* 34:356–361, 1991
17. Despres JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ: Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 334:952–957, 1996
18. Haffner SM, Valdez RA, Hazuda HH, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin resistance syndrome (syndrome X). *Diabetes* 41:715–722, 1992
19. Laakso M: How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 137:959–965, 1993
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
21. Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 334:374–381, 1996
22. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI: Assessment of fat-free mass using bioelectrical impedance measurements of the human body. *Am J Clin Nutr* 41:810–817, 1985
23. Bonora E, Del Prato S, Bonadonna R, Gulli G, Solini A, Shank M, Ghiatas A, Lancaster J, Kilcoyne R, Alyassin A, DeFronzo R: Total body fat content and fat topography are associated differently with in vivo glucose metabolism in nonobese and obese nondiabetic women. *Diabetes* 41:1151–1159, 1992
24. Hales CN, Randle PJ: Immunoassay of insulin with insulin-antibody precipitate. *Biochem J* 88:137–144, 1963
25. Kiechl S, Willeit S, Poewe S, Egger G, Oberhollenzer F, Muggeo M, Bonora E: Insulin sensitivity and regular alcohol consumption: large, prospective, cross-sectional population study (Bruneck Study). *BMJ* 313:1040–1044, 1996
26. Bonora E, Willeit J, Kiechl S, Oberhollenzer F, Egger G, Bonadonna R, Muggeo M: Relationship between insulin and carotid atherosclerosis in the general population: the Bruneck Study. *Stroke* 28:1147–1152, 1997
27. Bray GA: An approach to the classification and evaluation of obesity. In *Obesity*. Björntorp P, Brodoff BN, Eds. Philadelphia, Lippincott, 1992, p. 294–308
28. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
29. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the second report of the National Cholesterol Education Program (NCEP). *JAMA* 269:3015–3023, 1993
30. Consensus Conference: Treatment of hypertriglyceridemia. *JAMA* 251:1196–1201, 1984
31. Saggiani F, Pilati S, Targher G, Branzi P, Muggeo M, Bonora E: Serum uric acid and related factors in 500 hospitalized subjects. *Metabolism* 45:1557–1561, 1996
32. Subcommittee of WHO/ISH Mild Hypertension Liaison Committee: Summary of 1993 World Health Organisation International Society hypertension guidelines for the management of mild hypertension. *BMJ* 307:1541–1546, 1993

33. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH: The natural history of impaired glucose tolerance in the Pima Indians. *N Engl J Med* 319:1500–1507, 1988
34. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. *Diabetes Care* 13:610–630, 1990
35. Lewis GF, Uffelman KD, Szeto LW, Steiner G: Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL ApoB production in normal weight and obese individuals. *Diabetes* 42:833–842, 1993
36. Garg A: Insulin resistance in the pathogenesis of dyslipidemia. *Diabetes Care* 19:387–389, 1996
37. Quinones A, Santoro D, Natali A, Sampietro T, Boni C, Masoni A, Buzzigoli G, Ferrannini E: Insulin sensitivity in familial hypercholesterolemia. *Metabolism* 42:1359–1364, 1993
38. Karhapee P, Voutilainen E, Kovanen PT, Laakso M: Insulin resistance in familial and nonfamilial hypercholesterolemia. *Arterioscl Thromb Vasc Biol* 13:41–47, 1993
39. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, Travia D, Zenti MG, Branzi P, Santi L, Muggeo M: Relationship of fasting insulin to cardiovascular risk factor is already present in young men: the Verona Young Men Atherosclerosis Risk Factor Study. *Eur J Clin Invest* 27:248–254, 1997
40. Facchini F, Chen YDI, Hollenbeck CB, Reaven GM: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance and plasma uric acid concentration. *JAMA* 266:3008–3011, 1991
41. Quinones Galvan A, Natali A, Baldi S, Ferrannini E: Effect of insulin on uric acid excretion in humans. *Am J Physiol* 268:E1–E5, 1995
42. Reaven GM: Banting Lecture 1987: role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
43. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G, on behalf of the European Group for the Study of Insulin Resistance (EGIR): Insulin resistance and hypersecretion in obesity. *J Clin Invest* 100:1166–1173, 1997
44. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R, for the IRAS Investigators: Insulin sensitivity and atherosclerosis. *Circulation* 93:1809–1817, 1996
45. Bonora E, Tessari R, Micciolo R, Zenere M, Targher G, Padovani R, Falezza G, Muggeo M: Intimal-medial thickness of the carotid artery in nondiabetic and non-insulin-dependent diabetic patients: relationship with insulin resistance. *Diabetes Care* 20:627–631, 1997
46. Clausen JO, Borch-Johnsen K, Ibsen H, Bergman RN, Hougaard P, Winther K, Pedersen O: Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy Caucasians: analysis of the impact of gender, body fat, physical fitness, and life-style factors. *J Clin Invest* 98:1195–1209, 1996
47. Beard JC, Bergman RN, Ward WK, Porte DP Jr: The insulin sensitivity index in nondiabetic man: correlation between clamp-derived and IVGTT-derived values. *Diabetes* 35:362–369, 1986
48. Bergman RN, Prager R, Volund A, Olefsky JM: Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest* 79:790–800, 1987
49. Groop LC: Drug treatment of non-insulin-dependent diabetes mellitus. In *Textbook of Diabetes*. Pickup J, Williams G, Eds. Oxford, U.K., Blackwell Science, 1997, p. 38.1–38.18
50. Yoshioka N, Kuzuya T, Matsuda A, Taniguchi M, Iwamoto Y: Serum proinsulin levels at fasting and after oral glucose load in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 31:355–360, 1988
51. Phillips DIW, Clark PM, Hales CN, Osmond C: Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med* 11:286–292, 1994

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