Relationship between obesity, insulin resistance, and coronary heart disease risk

Fahim Abbasi, Byron William Brown, Jr, Cindy Lamendola, Tracey McLaughlin,
and Gerald M. Reaven

J. Am. Coll. Cardiol. 2002;40;937-943

Journal of the American College of Cardiology
© 2002 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 40, No. 5, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)02051-X

Obesity, Diabetes, and Heart Disease

Relationship Between Obesity, Insulin Resistance, and Coronary Heart Disease Risk

Fahim Abbasi, MD,* Byron William Brown, Jr, PhD,† Cindy Lamendola, MSN, ANP,*
Tracey McLaughlin, MD,* Gerald M. Reaven, MD*
Stanford, California

OBJECTIVES The study goals were to: 1) define the relationship between body mass index (BMI) and insulin resistance in 314 nondiabetic, normotensive, healthy volunteers; and 2) determine the relationship between each of these two variables and coronary heart disease (CHD) risk factors.

BACKGROUND The importance of obesity as a risk factor for type 2 diabetes and hypertension is well-recognized, but its role as a CHD risk factor in nondiabetic, normotensive individuals is less well established.

METHODS Insulin resistance was quantified by determining the steady-state plasma glucose (SSPG) concentration during the last 30 min of a 180-min infusion of octreotide, glucose, and insulin. In addition, nine CHD risk factors: age, systolic blood pressure, diastolic blood pressure (DBP), total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein cholesterol concentrations, and glucose and insulin responses to a 75-g oral glucose load were measured in the volunteers.

RESULTS The BMI and the SSPG concentration were significantly related ($r = 0.465$, $p < 0.001$). The BMI and SSPG were both independently associated with each of the nine risk factors. In multiple regression analysis, SSPG concentration added modest to substantial power to BMI with regard to the prediction of DBP, HDL cholesterol and TG concentrations, and the glucose and insulin responses.

CONCLUSIONS Obesity and insulin resistance are both powerful predictors of CHD risk, and insulin resistance at any given degree of obesity accentuates the risk of CHD and type 2 diabetes. (J Am Coll Cardiol 2002;40:937–43) © 2002 by the American College of Cardiology Foundation

Results of the Third National Health and Nutrition Examination Survey (NHANES III) have documented the fact that obesity has become a national epidemic (1). The importance of obesity as a risk factor for type 2 diabetes (2) and hypertension (3) has been well recognized, but its role as a coronary heart disease (CHD) risk factor in nondiabetic, normotensive individuals has been less well established. In this context, two issues seemed worthy of investigation in order to define more clearly the relationship between obesity and CHD. Although insulin resistance is often considered to be the link between obesity and type 2 diabetes, hypertension, and CHD risk, there is evidence that obese and overweight individuals can also be insulin-sensitive (4–6). Thus, the first goal of this study was to define the relationship between resistance to insulin-mediated glucose disposal and body mass index (BMI) in a large group of healthy, nondiabetic volunteers.

See page 944

Our second goal was to clarify the relative impact of obesity, per se, as distinguished from insulin resistance, on CHD risk factors. Given the difficulty in achieving success in weight control programs (7), it would be helpful to identify a subset of obese individuals who would benefit the most from weight loss and, therefore, be given the highest priority in weight loss programs.

The present report describes the relationship between BMI and insulin resistance in 314 nondiabetic, normotensive, healthy volunteers and defines the association of conventional CHD risk factors with obesity and insulin resistance.

METHODS

The data to be analyzed represent information gathered on 314 volunteer subjects, 186 women and 128 men, who had participated in our research studies from 1990 to 1998. Subjects included in the evaluation had no history of diabetes, CHD, or hypertension. In addition, they had normal findings upon physical examination and routine laboratory tests and were nondiabetic (8). The majority of participants were Caucasian (77%), with a small percentage of individuals of Asian (12%), Hispanic (10%), and African ancestries (1%). The volunteers had a mean ± SD age of 46

From the Departments of *Medicine and †Health Research and Policy, Stanford University School of Medicine, Stanford, California. Supported by Research Grants from the National Institutes of Health (RR-00070 and HL-08506).

Manuscript received August 27, 2001; revised manuscript received March 19, 2002, accepted June 4, 2002.

Abbreviations and Acronyms

BMI = body mass index
CHD = coronary heart disease
DBP = diastolic blood pressure
EGIR = European Group for the Study of Insulin Resistance
HDL = high-density lipoprotein
LDL = low-density lipoprotein
NHANES = National Health and Nutrition Examination Survey
SBP = systolic blood pressure
SSPG = steady-state plasma glucose
SSPI = steady-state plasma insulin
TG = triglycerides

± 13 years (range, 19 to 79) and BMI of 25.2 ± 3.8 kg/m^2 (range, 18.5 to 34.6).

Subjects were weighed on an electronic scale to the nearest 0.01 kg in hospital garments, height was measured to the nearest 0.01 cm without shoes, and BMI was calculated by dividing weight in kilograms by the square of the height in meters. Fasting plasma glucose and insulin concentrations were measured before and 30, 60, 120, and 180 min after the ingestion of a 75-g oral glucose challenge. The total integrated glucose and insulin responses were quantified by calculating the glucose and insulin area under the curve by use of the trapezoidal method. The analytical methods used for determining plasma glucose and insulin concentrations were similar over the duration of the study, as were those used for the determination of fasting concentrations of total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol (9–11). Insulin-mediated glucose disposal was estimated by a modification of the insulin suppression test (12) as introduced and validated by our research group (13). After an overnight fast, an intravenous catheter was placed in each arm of the patient. One arm was used for the administration of a 180-min infusion of octreotide, insulin, and glucose, and the other arm was used for collecting blood samples. Blood was sampled every 30 min initially and then at 10-min intervals from 150 to 180 min of the infusion to determine the steady-state plasma insulin (SSPI) and glucose concentrations for each individual. Because SSPI concentrations are similar for all subjects, the steady-state plasma glucose (SSPG) concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; the higher the SSPG, the more insulin-resistant is the individual.

The population was divided into three categories of BMI as proposed by the National Institutes of Health (14): normal weight (18.5 to 24.9 kg/m^2); overweight (25.0 to 29.9 kg/m^2); and obesity class I (30.0 to 34.9 kg/m^2). When this was done, our study population closely resembled the distribution of BMI in NHANES III, containing 52.5%, 32.1%, and 15.3% of individuals defined as being normal weight, overweight, and obese (15), compared with values of 43.6%, 32.6%, and 14.3%, respectively, for the same groups in NHANES III (1,15).

Data are expressed as mean ± SE. In each of the three BMI categories, means of BMI, SSPG, and the nine CHD risk factors (age, systolic blood pressure [SBP], diastolic blood pressure [DBP], total cholesterol, TG, HDL cholesterol, LDL cholesterol, glucose response, and insulin response) were compared using one-way analysis of variance.

The relationship between BMI and SSPG concentration was depicted in the form of a scatter plot, and Pearson and Spearman correlation coefficients were calculated. Individuals were defined as insulin-sensitive and insulin-resistant if they were in the lower (SSPG $<$4.66 mmol/l) and upper (SSPG $>$8.38 mmol/l) SSPG tertiles of the sample, respectively.

Simple and partial (adjusting for sex) correlation coefficients were calculated, first between each of the nine CHD risk factors and BMI, and then between each of the nine CHD risk factors and SSPG.

Multiple regression analyses were performed to evaluate whether the prediction of each of the nine CHD risk factors from the level of BMI would be modified if the degree of insulin resistance (SSPG) and an interaction between obesity (BMI) and insulin resistance (SSPG) were known in addition to the BMI. Two regression models were employed to evaluate these relationships. In model A, each risk factor was regressed on BMI and SSPG jointly. In model B, each risk factor was regressed on BMI, SSPG, and an interaction term. The interaction term was calculated by multiplying BMI and SSPG for each individual. Furthermore, using the results of regression model B, each of the nine CHD risk factors and BMI were graphed as continuous variables, while holding SSPG constant at three levels, namely, the means of the lower (insulin-sensitive), intermediate, and upper (insulin-resistant) SSPG tertiles of the sample.

RESULTS

The demographic characteristics of three obesity categories are listed in Table 1, as are the values for SSPG concentration. The ages and gender distributions of the three groups were similar. The BMI values were significantly different, and the higher the BMI category, the greater the SSPG concentration ($p < 0.05$). Table 1 also presents the values for the CHD risk factors assessed in the three experimental groups, and it can be seen that all of these variables worsen as BMI increases.

The relationship between BMI and SSPG concentration in the entire population is shown in Figure 1. Although the Pearson correlation coefficient between the two variables was of statistically significant ($r = 0.465$, $p < 0.001$) magnitude, only 22% (r^2) of the variability in SSPG concentrations within this sample could be attributed to the association with BMI. It should be noted that the nonparametric (Spearman correlation coefficient) relationship be-

Table 1. Demographic and Metabolic Characteristics of Volunteers by BMI Group

Variable	Normal Weight (n = 165)	Overweight (n = 101)	Obesity Class I (n = 48)	p Value
Age (yrs)	44 ± 1 (19–79)	48 ± 1 (19–71)	47 ± 2 (26–75)	0.1
Gender (female/male %)	61/39	55/45	60/40	0.64
BMI (kg/m^2)	22.2 ± 0.1 (18.5–24.9)	27.0 ± 0.1 (25.0–29.9)	31.7 ± 0.2 (30.0–34.6)	< 0.001
SSPG (mmol/l)	5.57 ± 0.20 (1.89–13.99)	8.34 ± 0.41 (1.39–17.15)	9.82 ± 0.61 (2.89–18.43)	< 0.05
SBP (mm Hg)	114 ± 1 (82–139)	118 ± 1 (90–139)	121 ± 1 (104–139)	< 0.01
DBP (mm Hg)	71 ± 1 (48–89)	74 ± 1 (50–89)	73 ± 1 (52–88)	0.03
Total cholesterol (mmol/l)	4.51 ± 0.07 (2.10–6.76)	5.02 ± 0.09 (3.08–7.77)	5.15 ± 0.13 (3.52–7.80)	< 0.001
TG (mmol/l)	0.92 ± 0.04 (0.29–5.01)	1.34 ± 0.06 (0.37–2.99)	1.69 ± 0.13 (0.52–5.07)	< 0.001
HDL cholesterol (mmol/l)	1.43 ± 0.03 (0.60–2.51)	1.26 ± 0.03 (0.73–2.36)	1.13 ± 0.03 (0.73–1.74)	< 0.001
LDL cholesterol (mmol/l)	2.69 ± 0.06 (1.08–4.77)	3.15 ± 0.08 (1.42–6.28)	3.26 ± 0.13 (1.79–5.57)	< 0.001
Glucose response (mmol/l·3 h)	17.07 ± 0.26 (10.24–28.35)	18.92 ± 0.35 (9.98–29.76)	19.58 ± 0.71 (11.38–34.13)	< 0.001
Insulin response (pmol/l·3 h)	809 ± 33 (139–2,580)	1,214 ± 85 (365–4,990)	1,682 ± 214 (346–8,523)	< 0.001

Data are given as mean ± SE (range) or percentage of subjects; p value is for the differences among the three BMI groups by one-way analysis of variance, except for gender distribution differences, calculated using chi-square test.

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density cholesterol; LDL = low-density cholesterol; SBP = systolic blood pressure; SSPG = steady-state plasma glucose; TG = triglycerides.

tween the two variables was similar in magnitude (ρ = 0. 441, $p < 0.001$). Furthermore, SSPG values varied widely across the BMI range; obese individuals (BMI >30.0 kg/m^2) were insulin-sensitive, and insulin resistance occurred in normal weight individuals (BMI <25.0 kg/m^2). Indeed, approximately 25% of insulin-resistant individuals were of normal weight, and the same proportion was obese.

Table 2 shows the simple and partial (adjusting for sex) correlation coefficients between BMI and SSPG and each of the nine CHD risk factors. Although these relationships were all statistically significant, there were notable differences in their magnitude. The BMI correlations were higher than SSPG correlation for age, SBP, total cholesterol, and LDL cholesterol. On the other hand, SSPG correlations were higher for DBP, TG, HDL cholesterol, glucose response, and insulin response. It should be noted that these findings did not change when adjusted for differences in sex.

Table 3 shows the results of multiple regression analyses when the relationships between each CHD risk factor and BMI and SSPG were further quantified. The results using model A show that BMI was an independent predictor of SBP, total cholesterol, and LDL cholesterol concentrations, whereas SSPG was not. Conversely, SSPG was an independent predictor of DBP and glucose response, whereas BMI was not. Furthermore, both BMI and SSPG were independent predictors of TG, HDL cholesterol, and insulin response; however, SSPG was a stronger predictor of these risk factors as indicated by higher, and statistically significant, standardized regression coefficient values. Finally, the results of regression model B provide additional insights into these relationships, showing that the interaction term was the only independent predictor of glucose response and insulin response, whereas the interaction term, SSPG, and BMI all independently predicted HDL cholesterol.

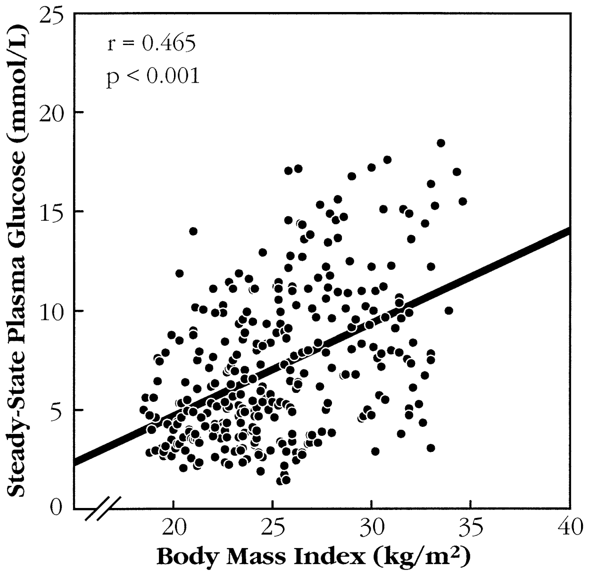

Figure 1. Relationship between body mass index and steady-state plasma glucose.

The results of multiple regression analyses using model B are graphically presented in Figure 2. In each panel, the regression lines describe the expected CHD risk factor as a function of obesity (BMI) at the mean SSPG concentration for the insulin-resistant (11.68 mmol/l), intermediate (6.33 mmol/l), and insulin-sensitive (3.37 mmol/l) SSPG tertiles.

Table 2. Simple and Partial Correlation Coefficients (r) Between Coronary Heart Disease Risk Factors, BMI, and SSPG

	BMI		SSPG	
Risk Factors	Simple	Partial	Simple	Partial
Age	0.189*	0.180*	0.106†	0.113*
SBP	0.286	0.278	0.160*	0.168*
DBP	0.139*	0.125*	0.202	0.216
Total cholesterol	0.348	0.349	0.242	0.243
TG	0.444	0.437	0.507	0.520
HDL cholesterol	−0.385	−0.382	−0.410	−0.461
LDL cholesterol	0.361	0.355	0.223	0.229
Glucose response	0.306	0.303	0.573	0.577
Insulin response	0.380	0.379	0.630	0.631

Partial correlation coefficients were calculated after adjusting for differences in gender; all p values are <0.001 except for *$p < 0.05$ and †$p = 0.16$.

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density cholesterol; LDL = low-density cholesterol; SBP = systolic blood pressure; SSPG = steady-state plasma glucose; TG = triglycerides.

Table 3. Multiple Regression Analysis of the Relationship Between the CHD Risk Factors With BMI and SSPG Jointly, Without an Interaction Term (Model A) and With the Interaction Term (Model B)

	Model A		Model B		
CHD Risk Factors	**BMI**	**SSPG**	**BMI**	**SSPG**	**BMI × SSPG**
Age	R_A = 0.190			R_B = 0.190	
β	0.178	0.023	0.183	0.043	−0.023
SE	0.215	0.012	0.428	0.076	0.003
p	0.005	0.711	0.145	0.915	0.961
SBP	R_A = 0.288			R_B = 0.290	
β	0.27	0.035	0.205	−0.207	0.280
SE	0.185	0.01	0.368	0.066	0.002
p	<0.001	0.573	0.094	0.601	0.537
DBP	R_A = 0.208			R_B = 0.210	
β	0.058	0.175	0.105	0.349	−0.202
SE	0.143	0.008	0.284	0.051	0.002
p	0.357	0.006	0.401	0.388	0.663
Total cholesterol	R_A = 0.358			R_B = 0.359	
β	0.301	0.098	0.244	−0.103	0.235
SE	0.561	0.032	1.115	0.198	0.007
p	<0.001	0.117	0.049	0.788	0.596
TG	R_A = 0.556			R_B = 0.557	
β	0.260	0.382	0.196	0.154	0.267
SE	0.860	0.049	1.709	0.302	0.011
p	<0.001	<0.001	0.077	0.655	0.501
HDL cholesterol	R_A = −0.463			R_B = −0.477	
β	−0.246	−0.293	−0.468	−1.08	0.922
SE	0.195	0.011	0.386	0.068	0.003
p	<0.001	<0.001	<0.001	0.003	0.029
LDL cholesterol	R_A = 0.365			R_B = 0.366	
β	0.330	0.065	0.347	0.128	−0.073
SE	0.505	0.029	1.009	0.179	0.007
p	<0.001	0.292	0.005	0.740	0.870
Glucose response	R_A = 0.575			R_B = 0.584	
β	0.051	0.549	−0.144	−0.171	0.836
SE	0.947	0.052	1.872	0.334	0.012
p	0.332	<0.001	0.165	0.609	0.030
Insulin response	R_A = 0.638			R_B = 0.649	
β	0.110	0.579	−0.123	−0.283	0.999
SE	1.628	0.090	3.203	0.571	0.021
p	0.026	<0.001	0.208	0.368	0.006

β = standardized regression coefficient; BMI = body mass index; CHD = coronary heart disease; DBP = diastolic blood pressure; HDL = high-density cholesterol; LDL = low-density cholesterol; R_A = multiple correlation coefficient for model A; R_B = multiple correlation coefficients for model B; SBP = systolic blood pressure; SSPG = steady-state plasma glucose; TG = triglycerides.

The figure shows that increasing levels of SSPG did not particularly modify the predicted SBP, LDL cholesterol, and total cholesterol. On the other hand, the predicted DBP, glucose response, and more strikingly, TG, HDL cholesterol, and insulin response were clearly higher at the insulin-resistant SSPG concentration.

DISCUSSION

Relationship between obesity and insulin resistance. The results of the current, population-based study provide additional insight into the relationship between obesity and insulin resistance and are reasonably similar to the only published study (4) in which this relationship has been evaluated in a large number of individuals using a specific method to determine insulin-mediated glucose disposal. In addition to supporting previous results (16–18) that differences in weight modulate insulin action, the data presented provide a quantitative estimate of the role of obesity in regulating insulin-mediated glucose disposal. The relationship between BMI and SSPG shown in Figure 1 and Table 1 indicates that only approximately 22% of the variability in SSPG concentration (r^2) in this healthy volunteer population can be attributed to differences in BMI, an estimate that is consistent with the report (4) of the European Group for the Study of Insulin Resistance (EGIR). This group quantified insulin action in 1,146 nondiabetic, normotensive individuals with the euglycemic, hyperinsulinemic clamp, and it also defined insulin resistance as the value of insulin-mediated glucose disposal in the lowest 10% of the normal weight population (BMI <25.0 kg/m^2). With this criterion they found 26% of the obese individuals (BMI > 29.0 kg/m^2) to be insulin-resistant. This estimate is similar

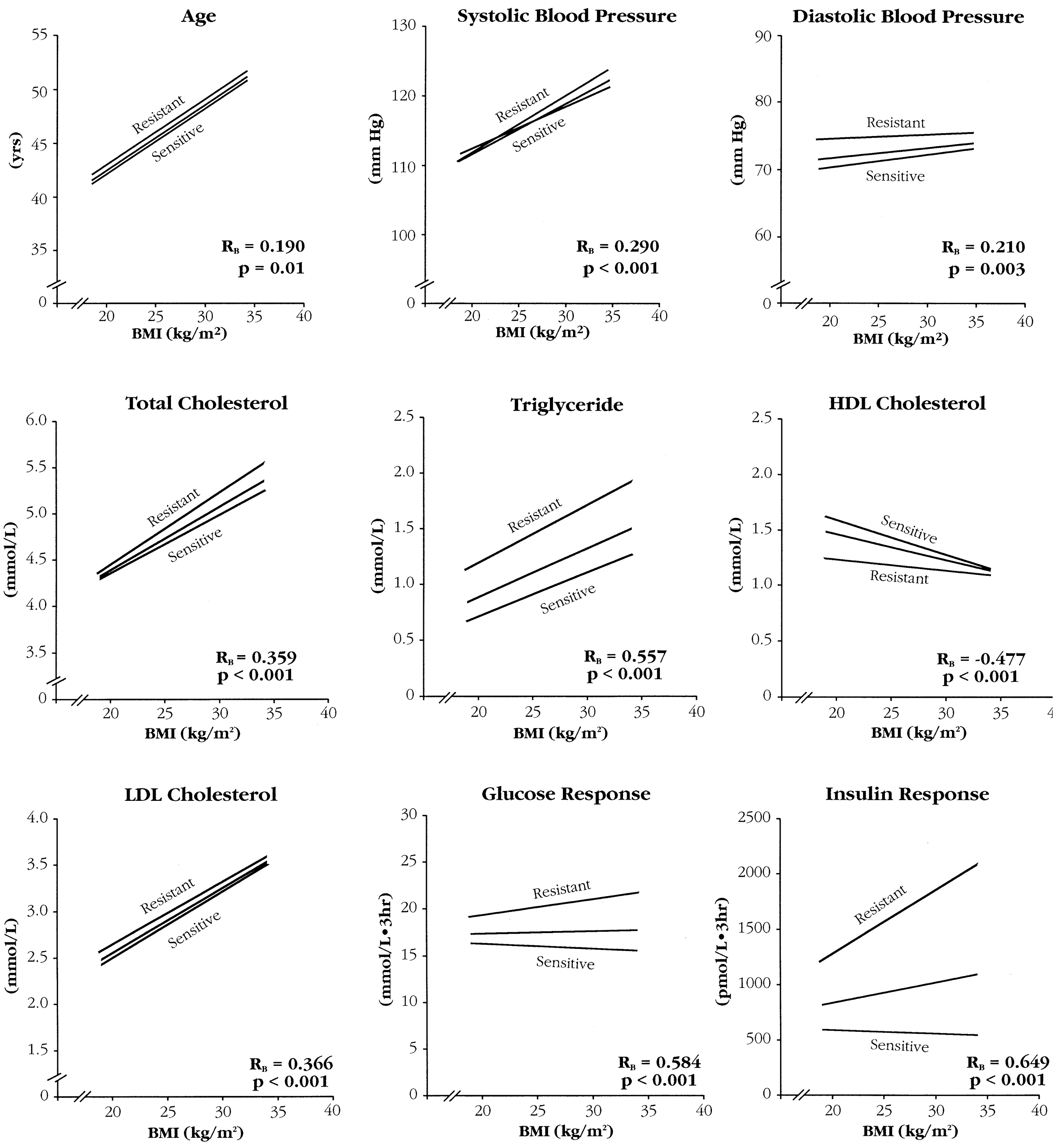

Figure 2. Graphic representation of the relationship between body mass index (BMI), steady-state plasma glucose, and coronary heart disk risk factors for regression model B. Dependent variables: coronary heart disease risk factors (age, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, glucose response, and insulin response). Independent variables: BMI, steady-state plasma glucose, and the interaction term. R_B = multiple correlation coefficient for the analyses based on regression model B.

to our finding that only 25% of our population in the upper tertile of insulin resistance had a BMI >30.0 kg/m^2. Similar quantitative estimates of the magnitude of the relationship between obesity and insulin resistance can be found in a case-control study involving both Pima Indians and Caucasians (18) in which approximately 25% of the variability in insulin action could be ascribed to differences in body weight. Because these studies excluded patients with diabetes and/or hypertension, syndromes known to be both more common in obese individuals and associated with impaired insulin action independent of obesity (19), the estimates of the relationship between obesity and insulin resistance are applicable only to individuals without any disease known to affect insulin action.

One important caveat that must be made as to our estimate of the magnitude of the relationship between obesity and insulin-mediated glucose disposal is the use of BMI as the measure of obesity. This decision was based upon our attempt to relate our findings to the NHANES III results, but it should be noted that the conclusions of the EGIR investigators (4) was independent of the estimates of obesity used in that "neither the waist circumference, nor the waist-to-hip ratio, indices of body fat distribution, was related to insulin sensitivity after adjustment for age, gender, and BMI."

Relationship between obesity, insulin resistance, and type 2 diabetes. The results of this study provide relevant information concerning the link between obesity and insulin resistance and the development of type 2 diabetes. Several prospective studies have shown that degree of insulin resistance and/or hyperinsulinemia are strong predictors of type 2 diabetes in normal glucose tolerant individuals (20–25). It is obvious from Figure 2 that, at any given BMI, the most insulin-resistant tertile had plasma insulin concentrations that were three to four times higher than those in the most insulin-sensitive tertile. It should also be noted that the individuals in the most insulin-resistant tertile were also the most glucose intolerant, a change that also increases their risk of developing type 2 diabetes (20). Based upon these considerations, it can be concluded that overweight/obese individuals are not at equal risk to develop type 2 diabetes, and those in the lowest insulin-resistant tertile are at less risk of developing type 2 diabetes than an insulin-resistant individual of any weight.

Relationship between obesity, insulin resistance, and CHD. The results presented also provide considerable insight into the relationship between obesity, insulin resistance, and CHD risk. Insulin resistance and/or compensatory hyperinsulinemia have been shown to predict CHD in nondiabetics (26–30), although it is not clear if this is a direct effect or secondary to the risk factors present in these individuals (31). The metabolic abnormalities most closely related to insulin resistance are hyperinsulinemia, some degree of glucose intolerance, hypertriglyceridemia, and a low HDL cholesterol concentration (31), changes that have been shown to increase CHD risk (26–34). In our study we have demonstrated that, for a given level of obesity, these metabolic abnormalities are clearly accentuated in the most insulin-resistant tertile (Table 3 and Fig. 2). Thus, whether it is insulin resistance, per se, or its most common manifestations that increase CHD risk in insulin-resistant individuals, these changes are not present in obese individuals who are insulin-sensitive.

Conclusions. The results presented have reaffirmed the fact that the greater the BMI, the more insulin-resistant the individual. At the same time our results show that overweight/obese individuals can be insulin-sensitive and that normal weight subjects can be insulin-resistant. In addition, we have differentiated between the relative impact of overweight/obesity and insulin resistance on CHD risk factors, demonstrating that insulin resistance at any given BMI accentuates the risks of both type 2 diabetes and CHD. Implications of these findings are self-evident; the most intensive efforts to reduce risk of type 2 diabetes and CHD in overweight/obese individuals should be focused on those individuals who are also insulin-resistant.

Reprint requests and correspondence: Dr. Gerald M. Reaven, Falk CVRC Stanford University School of Medicine, 300 Pasteur Drive, Stanford, California 94305-5406. E-mail: greaven@cvmed.Stanford.edu.

REFERENCES

1. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. Int J Obes Relat Metab Disord 1998;22:39–47.
2. West KM, Kalbfleisch JM. Influence of nutritional factors on prevalence of diabetes. Diabetes 1971;20:99–108.
3. Havlik RJ, Hubert HB, Fabsitz RR, Feinleib M. Weight and hypertension. Ann Intern Med 1983;98:855–9.
4. 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 1997;100:1166–73.
5. McLaughlin T, Abbasi F, Carantoni M, Schaaf P, Reaven GM. Differences in insulin resistance do not predict weight loss in response to hypocaloric diets in healthy obese women. J Clin Endocrinol Metab 1999;84:578–81.
6. Jones CNO, Abbasi F, Carantoni M, Polonsky KS, Reaven GM. Roles of insulin resistance and obesity in regulation of plasma insulin concentrations. Am J Physiol Endocrinol Metab 2000;278:E501–8.
7. Wadden JA. Treatment of obesity by moderate and severe caloric restriction: results of clinical trials. Ann Intern Med 1993;119:688–93.
8. American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–97.
9. Hollenbeck CB, Johnston P, Varasteh BB, Chen Y-DI, Reaven GM. Effects of metformin on glucose insulin and lipid metabolism in patients with mild hypertryglyceridaemia and non-insulin dependent diabetes by glucose tolerance test criteria. Diabete Metab 1991;17:483–9.
10. Reaven GM, Chen Y-DI, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense, low density lipoprotein particles. J Clin Invest 1993;92:141–6.
11. Jeppesen J, Schaaf P, Jones C, Zhou M-Y, Chen Y-DI, Reaven GM. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. Am J Clin Nutr 1997;65:1027–33.
12. Pei D, Jones CNO, Bhargava R, Chen Y-DI, Reaven GM. Evaluation of octreotide to assess insulin-mediated glucose disposal by the insulin suppression test. Diabetologia 1994;37:843–5.
13. Greenfield MS, Doberne L, Kraemer FB, Tobey TA, Reaven GM. Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. Diabetes 1981;30:387–92.
14. Report of a WHO Consultation. WHO Technical Report Series, No. 894. Obesity: preventing and managing the global epidemic: report of a WHO Consultation on Obesity, Geneva, June 3–5, 1997. Geneva: World Health Organization, 1998.
15. Kuczmarski RJ, Carroll MD, Flegal KM, Troiano RP. Varying body mass index cutoff points to describe overweight prevalence among U.S adults: NHANES III (1988 to 1994). Obes Res 1997;5:542–8.
16. Rabinowitz D, Zierler KL. Forearm metabolism in obesity and its response to intraarterial insulin: characterization of insulin resistance and evidence for adaptative hyperinsulinism. J Clin Invest 1962;12:2173–81.
17. Olefsky JM, Reaven GM, Farquhar JW. Effects of weight reduction on obesity: studies of carbohydrate and lipid metabolism. J Clin Invest 1974;53:64–76.

18. Bogardus C, Lillioja S, Mott D, Reaven G, Kashiwagi A, Foley J. Relationship between obesity and maximal insulin stimulated glucose uptake in vivo and in vitro in Pima Indians. J Clin Invest 1984;73: 800–5.
19. Maheux P, Jeppesen J, Sheu WH-H, et al. Additive effects of obesity, hypertension, and type 2 diabetes on insulin resistance. Hypertension 1994;24:695–8.
20. Sicree RA, Zimmet PZ, King HOM, Coventry JS. Plasma insulin response among Nauruans: prediction of deterioration in glucose tolerance over 6 years. Diabetes 1987;36:179–86.
21. Saad MF, Pettit DJ, Mott DM, Knowler WC, Nelson RG, Bennett PH. Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. Lancet 1989;1:1356–9.
22. Haffner SM, Stern MP, Mitchell BD, Hazua HP, Patterson JK. Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity and body-fat distribution. Diabetes 1990;39:283–8.
23. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Khan CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of the diabetic parents. Ann Intern Med 1990;113:909–15.
24. Lilloja S, Mott DM, Spraul M, et al. Insulin resistance and insulin secretory dysfunction as precursors for non-insulin-dependent diabetes mellitus. N Engl J Med 1993;329:1988–92.
25. Everhart J, Knowler WC, Bennett PH. Incidence and risk factors for noninsulin-dependent diabetes. In: Diabetes in America. Harris MI, Hamman RF, editors. Bethesda, MD: NIH publ. 1985: IV–1.
26. Pyorala K. Relationship of glucose tolerance and plasma insulin in the incidence of coronary heart disease: results from two population studies in Finland. Diabetes Care 1979;2:131–41.
27. Ducimetiere P, Eschwege JL, Papoz JL, et al. Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in middle-aged population. Diabetologia 1980; 19:205–10.
28. Depres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996;334:952–7.
29. Yip J, Facchini FS, Reaven GM. Resistance to insulin-mediated glucose disposal as a predictor of cardiovascular disease. J Clin Endocrinol Metab 1998;83:2773–6.
30. Zavaroni I, Bonini L, Gasparini P, et al. Hyperinsulinemia in a normal population as a predictor of non-insulin-dependent diabetes mellitus, hypertension, and coronary heart disease: the Barilla factory revisited. Metabolism 1999;48:989–94.
31. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
32. Vaccaro O, Ruth KJ, Stamler J. Relationship of postload plasma glucose to mortality with 19-yr follow-up. Diabetes Care 1992;13: 1328–34.
33. Miller GJ, Miller NE. Plasma-high-density-lipoprotein concentration and development of ischaemic heart disease. Lancet 1975;1:16–9.
34. Austin MA, Hoakanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 1998;81:7B–12B.

Relationship between obesity, insulin resistance, and coronary heart disease risk

Fahim Abbasi, Byron William Brown, Jr, Cindy Lamendola, Tracey McLaughlin, and Gerald M. Reaven

J. Am. Coll. Cardiol. 2002;40;937-943