Prevalence of Insulin Resistance and Associated Cardiovascular Disease Risk Factors Among Normal Weight, Overweight, and Obese Individuals

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Obese individuals tend to be both insulin resistant and at increased risk to develop cardiovascular disease (CVD). Given the increased prevalence of obesity in the US population, we thought it important to define the relationship between degree of obesity and insulin-mediated glucose disposal in the population at large, as well as the relationship between obesity, insulin resistance, and CVD risk in these individuals. To do this we quantified insulin-mediated glucose disposal in 465 healthy volunteers by determining the steady-state plasma glucose (SSPG) concentrations at the end of a 180-minute infusion of somatostatin, insulin, and glucose. Adiposity was estimated by body mass index (BMI) and the relationship between BMI and SSPG defined. In addition, a series of CVD risk factors were measured, including blood pressure, plasma glucose, and insulin concentrations, before and after 75 g of oral glucose, and fasting plasma lipid and lipoprotein concentrations. The results indicated that SSPG concentration and BMI were significantly correlated ($r = 0.54$, $P > .001$), and 36% of individuals in the most insulin-resistant tertile were obese (BMI $\geq$ 30.0 kg/m^2). However, 16% of those in the most insulin-resistant tertile were of normal weight (BMI < 25.0 kg/m^2). Although CVD risk factors were accentuated in general with progressive increases in either BMI or SSPG concentration, important differences were noted. Thus, the higher the SSPG concentration, the more the increase in plasma glucose, insulin, and triglyceride (TG) concentrations, whereas the greater the BMI, the higher the low-density lipoprotein concentration. Furthermore, while CVD risk factors increased significantly with each tertile of insulin resistance, significant differences in CVD risk were only apparent when the lowest BMI tertile was compared with the other 2, with the values in the middle and upper BMI differing from each other. These results show that while BMI and insulin resistance are related, they are not synonymous, and that they make independent and different contributions to increasing CVD risk.

MEASUREMENTS OF body mass index (BMI) have been used[1] to define the population at large as being of normal weight (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25.0 to 29.9 kg/m^2), or obese (BMI $\geq$ 30 kg/m^2). Application of these criteria to the results of the Third National Health and Nutrition Examination Survey (NHANES III) indicated that only 43.6% of those surveyed were of normal weight.[2] Given the importance of obesity as a risk factor for hypertension, cardiovascular disease (CVD), and type 2 diabetes,[3-5] the increase in the prevalence of obesity is a cause of great concern. In this context, there is evidence that: (1) insulin-mediated glucose disposal is decreased in obese individuals[6,7]; (2) this defect increases the risk of developing hypertension, CVD, and type 2 diabetes[8-13]; and (3) weight loss will enhance insulin sensitivity.[6,14,15] Given the enormity of this problem, it is disappointing that only approximately 50% of physicians polled appeared to offer weight loss counseling to their patients.[16] There are undoubtedly many reasons for these findings, but it is highly likely that the sheer number of the overweight/obese population, and the difficulty in achieving weight loss,[17] are largely responsible for lack of physician enthusiasm to address weight control.

There are no simple answers to this dilemma, but as a first step, it might be useful to explore the relationship between BMI, degree of insulin resistance, and CVD risk. The current analysis was initiated to address this issue and had as its primary goals: (1) the quantitative description of the relationship between BMI and insulin-mediated glucose disposal in 465 nondiabetic, healthy individuals; and (2) determination of the extent to which BMI and insulin resistance are separate and independent entities that contribute to CVD risk.

MATERIALS AND METHODS

The experimental population consisted of 465 individuals who had volunteered for various studies by our research group between 1987 and 1999. They had all responded to advertisements in local newspaper requesting the participation of healthy volunteers in clinical research studies that had been approved by the Institutional Review Board of Stanford Medical Center. To be enrolled in these studies, subjects had to be in good general health as determined by history, physical examination, and chemical screening battery, nondiabetic,[18] and taking no drugs for the treatment of blood pressure, hyperglycemia, or dyslipidemia. Participants were primarily of Caucasian origin (77%), with a small percentage of individuals of Asian (12%), Hispanic (10%), and African ancestries (1%). The demographic characteristics of the 465 individuals evaluated were as follows (mean $\pm$ SEM): age 49 $\pm$ 6 years, BMI, 25.9 $\pm$ 2 kg/m^2; systolic blood pressure 127 $\pm$ 0.9 mm Hg; diastolic blood pressure 78 $\pm$ 0.6 mm Hg; and fasting plasma glucose 91 $\pm$ 1 mg/dL.

Subjects were evaluated at the Stanford General Clinical Research Center (GCRC) after giving written, informed consent. Plasma glucose and insulin concentrations were measured before and 30, 60, 120, and 180 minutes after the ingestion of a 75-g oral glucose challenge, and the areas under the curve (trapezoidal method) are referred to as "glucose response" and "insulin response." In addition, blood was obtained after an overnight fast for the determination of lipid and lipoprotein concentrations. The analytical methods used for determining plasma glucose and insulin concentrations were similar over the duration of the study, as were those used for measurement of cholesterol, triglyceride (TG),

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Table 1. Demographic Characteristics According to Tertile of SSPG

	Tertile 1 (n = 155)	Tertile 2 (n = 155)	Tertile 3 (n = 155)
SSPG (mg/dL)	66 ± 1	133 ± 2	236 ± 3
Age (yr)	46 ± 1	48 ± 1	51 ± 1
BMI (kg/m^2)	23.6 ± 0.2	25.6 ± 0.3	28.4 ± 0.3
Gender (M/F)	70/85	71/84	74/81

NOTE. Data are mean ± SEM.

high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentrations.[11,19]

On a separate admission to the GCRC, insulin-mediated glucose disposal was quantified by a modification[20] of the insulin suppression test as initially described by our research group[21] and shown to be highly correlated ($r = 0.93$) with the euglycemic, hyperinsulinemic clamp technique.[22] Briefly, after an overnight fast, an intravenous catheter was placed in each of the subjects' arms. One was used for administration of a 180-minute infusion of octreotide (250 μg/h), insulin (25 mU $\cdot$ m^{-2} $\cdot$ min^{-1}), and glucose (240 mg $\cdot$ m^{-2} $\cdot$ min^{-1}), and the other was used for collecting blood samples. Blood was sampled every 30 minutes initially and then at 10-minute intervals from 150 to 180 minutes of the infusion to determine the steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations for each individual. Because SSPI concentrations are similar for all subjects, the 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 the individual.

While insulin resistance is distributed continuously throughout the population, for the purposes of this analysis, SSPG values were classified as tertiles, with the most insulin-resistant tertile of primary clinical significance. This decision was based on the results of prospective studies showing that the incidence of several adverse clinical events associated with insulin resistance was significantly increased in individuals in the highest SSPG tertile at baseline, whereas those untoward consequences did not occur in the lowest SSPG tertile.[11,23] Table 1 presents the SSPG concentrations, age, BMI, and gender distribution of the 3 SSPG tertiles. It can be seen that the 3 groups were similar in terms of age and gender. However, by selection, the SSPG concentrations of each tertile are quite disparate. Finally, it is apparent that BMI values increased progressively from the lowest to the highest SSPG tertile.

To evaluate the relationship between insulin resistance and body mass, the association was first evaluated with SSPG and BMI as continuous measures. To obtain a more clinically meaningful description of this relationship, the population was subdivided into 3 groups based upon the BMI criteria outlined in a recent report from the National Institutes of Health[1] and applied to the NHANES III population.[2] Specifically, normal weight was defined as BMI $<$25.0 kg/m^2; overweight as BMI 25.0 to 29.9 kg/m^2; and obese as BMI 30.0 to 34.9 kg/m^2. The distribution of BMI values in our population was similar to that of NHANES III, consisting of the following: normal weight (43%), overweight (35%), and obese (18%). Because individuals with BMI $\geq$ 35 kg/m^2 comprised only 4% of the study population, they were excluded from analysis for statistical reasons. The distribution of BMI by category was then ascertained for each SSPG tertile, with the primary interest being the BMI distribution in the most insulin-resistant tertile, ie, the tertile associated with increased CVD risk.

To ascertain the impact of insulin resistance on CVD risk, CVD risk factors were evaluated across SSPG tertiles, adjusted for BMI, age, gender, and multiple comparisons. Similarly, to determine the impact of body mass on CVD risk, CVD risk factors were evaluated across BMI tertiles, adjusting for SSPG, age, gender, and multiple comparisons. BMI tertiles rather than clinical categories as defined above were used to ensure that group sizes were equal and that power to detect differences according to BMI group was maximized. Finally, to ascertain the relative independent contribution of insulin resistance and BMI to each CVD risk factor, multiple regression analysis was conducted for each factor as a function of BMI, SSPG, age, and gender.

Data are expressed as mean ± SEM. Pearson's correlation coefficient was determined to assess the strength of the association between BMI and SSPG and significance of association assessed with simple linear regression. Distribution of clinical BMI categories was determined for each SSPG tertile, as described. CVD risk factors were compared across SSPG tertiles with analysis of covariance, controlling for BMI, age and gender. CVD risk factors were also compared (using analysis of covariance) across tertiles of BMI, controlling for SSPG, age, and gender. Multiple linear regression analysis was performed for each CVD risk factor as a function of BMI and SSPG as continuous variables, as well as age and gender. P values were considered significant at a level of $P < .05$, and Tukey's adjustment for multiple comparisons was made. All analyses were performed using SAS, version 8e for windows (SAS Institute, Cary, NC).

RESULTS

Figure 1 illustrates the relationship between BMI and SSPG concentration in the entire volunteer population of 465 individuals. Although these data document the presence of a statistically significant relationship between these 2 variables ($r = 0.54$, $P < .001$), it is obvious that the SSPG concentrations are distributed continuously through the BMI range. Thus, not all normal weight individuals had low SSPG concentrations, nor did all obese individuals have high SSPG concentrations.

Table 2 represents our effort to provide a more quantitative view of the distribution of each of the BMI groups within the 3 SSPG tertiles. These data indicate that 30% of the individuals in the most insulin-sensitive tertile (tertile 1) were either overweight (25%) or obese (5%). Of those in the most insulin-

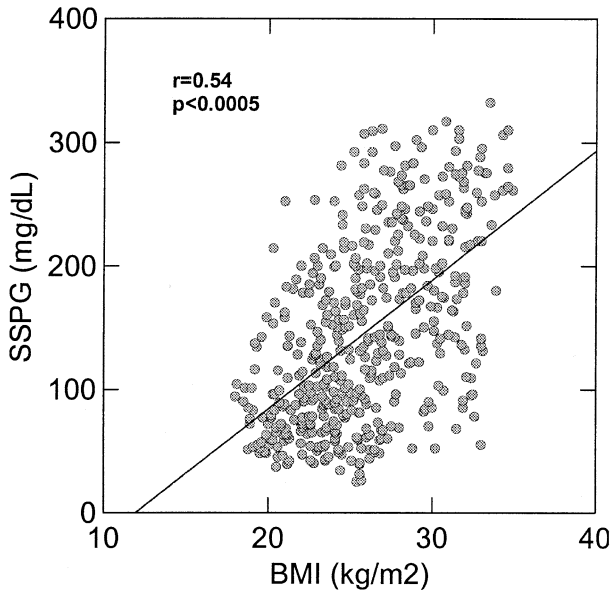

Fig 1. Relationship between BMI and SSPG.

Table 2. Distribution of BMI (kg/m^2) According to SSPG Tertile (number and percent)

BMI (kg/m^2)	Tertile 1 (%)	Tertile 2 (%)	Tertile 3 (%)
< 25.0	109 (70)	75 (48)	24 (16)
25.0-29.9	39 (25)	54 (35)	75 (48)
30.0-34.9	7 (5)	26 (17)	56 (36)
Total	155	155	155

resistant tertile, 36% were obese, with the remainder being either overweight (43%) or normal weight (16%).

Table 3 presents the mean values of the CVD risk factors in each of the SSPG tertiles, adjusted for differences in age, gender, and BMI. It is apparent from these results that the more insulin resistant the individual (SSPG tertile 3), the greater the magnitude of the abnormality in CVD risk factor, and the *P* value for trend was less than .001 in most cases. The only exception to this generalization was that LDL-C concentrations did not vary as a function of SSPG tertile. It should also be noted that all 3 SSPG tertiles were different from each other as regards diastolic blood pressure, plasma TG, and HDL-C concentrations, and the plasma glucose and insulin responses to the glucose challenge.

In symmetry with the analysis shown in Table 3, the impact of BMI on CVD risk factors, adjusted for differences in SSPG, gender, and age, is evaluated in Table 4. Similar to the results in Table 3, most of the CVD risk factors were also accentuated as a function of increasing tertile of BM. However, this was not true of the total plasma glucose and insulin responses to the oral glucose challenge. Furthermore, the results in Table 4 also differed from those in Table 3 in that pairwise comparisons revealed significant differences in CVD risk only between the lowest BMI tertile (BMI 21.7 $\pm$ 0.1 kg/m^2) and the middle (BMI 25.5 $\pm$ 0.1 kg/m^2) or highest (BMI 30.4 $\pm$ 0.2) BMI tertile, but not between the middle and highest BMI tertile.

Finally, multiple linear regression analysis was performed for each CVD marker as a function of BMI and SSPG as continuous, rather than categorical variables, adjusting for age and gender. The results, shown in Table 5, are consistent with the relationships in Tables 3 and 4 in that LDL-C was independently related to BMI, whereas SSPG concentration independently predicted plasma glucose and insulin responses to the oral glucose load. In examining the R^2 for each model (performed separately for each CVD risk marker), one can see that the variance in insulin, glucose, and TG is most highly explained by the combination of BMI and SSPG, whereas little of the variance in LDL-C concentration is explained by BMI and SSPG.

DISCUSSION

At the simplest level, the results of this study provide a quantitative description of the relationship between obesity and resistance to insulin-mediated glucose disposal. Before beginning a detailed discussion of the findings, the issue of the decision to use BMI as the index of obesity, rather than abdominal circumference, should be addressed. In the first place, BMI has been suggested by the National Institutes of Health as the means to classify individuals as being normal weight, overweight, or obese.[1] In addition, health care professionals are accustomed to determining height and weight, and these measurements are relatively simple to make, as well as being reasonably reproducible. Furthermore, values for BMI and abdominal circumference are highly correlated.[24,25] Finally, results of the European Group for the Study of Insulin Resistance concluded, on the basis of 1,146 specific measurements of insulin-mediated glucose disposal, that the relationship between adiposity and insulin resistance did not differ when abdominal circumference or BMI was the index of obesity.[7] Thus, we believe that the use of BMI to define the relationship between obesity and insulin resistance does not preclude the ability to generalize from our results.

The results in Table 1 and Fig 1 indicate that the greater the BMI, the more insulin resistant the individual. On the other hand, it is apparent from Table 2 that 30% of the individuals in the most insulin-sensitive tertile (SSPG tertile 1) were overweight/obese, and only 36 % of those in the most insulin-resistant tertile (SSPG tertile 3) were obese. Indeed, approximately 1 of 6 individuals in the most insulin-resistant tertile (SSPG tertile 3) was of normal weight. Thus, not all overweight/obese persons are insulin resistant, nor are normal-weight individuals universally insulin sensitive.

In addition to providing quantitative data as to the relation-

Table 3. Distribution of CVD Risk Factors According to SSPG Tertile (mean $\pm$ SEM) (2-way ANOVA adjusted for BMI, age, and gender)

Variable	Tertile of SSPG			*P* Value	
	1 (n = 155)	2 (n = 155)	3 (n = 155)	Trend	Pairwise*
SBP (mm Hg)	119 $\pm$ 1	125 $\pm$ 2	136 $\pm$ 2	<.0001	b, c
DBP (mm Hg)	73 $\pm$ 1	77 $\pm$ 1	84 $\pm$ 1	<.0001	a, b, c
LDL-C (mg/dL)	104 $\pm$ 3	115 $\pm$ 3	122 $\pm$ 3	.19	NS
HDL-C (mg/dL)	56 $\pm$ 1	50 $\pm$ 1	45 $\pm$ 1	<.0001	a, b
Triglycerides (mg/dL)	78 $\pm$ 3	111 $\pm$ 5	161 $\pm$ 7	<.0001	a, b, c
Fasting glucose (mg/dL)	87 $\pm$ 1	90 $\pm$ 1	95 $\pm$ 1	.006	b
Glucose response (mg/dL $\cdot$ 3 h)†	300 $\pm$ 4	330 $\pm$ 5	392 $\pm$ 6	<.0001	a, b, c
Fasting insulin (μU/mL)	7.9 $\pm$ 0.3	10.1 $\pm$ 0.4	15.7 $\pm$ 0.6	<.0001	b, c
Insulin response (μU/mL $\cdot$ 3 h)†	91 $\pm$ 3	152 $\pm$ 9	268 $\pm$ 12	<.0005	a, b, c

Abbreviation: NS, not significant.

*Pairwise differences with $P < .05$, a: 1 *v* 2; b: 1 *v* 3; c: 2 *v* 3.

†Area under the curve in response to 75-g oral glucose challenge.

Table 4. Distribution of CVD Risk Factors According to BMI Tertile (mean ± SEM) (ANCOVA adjusted for SSPG, age, and gender)

Variable	Tertile of BMI			*P* Value	
	1 (n = 155)	2 (n = 155)	3 (n = 155)	Trend	Pairwise*
BMI (kg/m^2)	21.7 ± 0.1	25.5 ± 0.1	30.4 ± 0.2	<.0001	a, b, c
SBP (mm Hg)	118 ± 1	128 ± 2	134 ± 2	<.0001	a, b
DBP (mm Hg)	73 ± 1	78 ± 1	82 ± 1	<.0001	a, b
LDL-C (mg/dL)	110 ± 3	116 ± 3	124 ± 3	<.0001	a, b
HDL-C (mg/dL)	56 ± 1	49 ± 1	45 ± 1	.002	a, b
Triglycerides (mg/dL)	86 ± 5	117 ± 5	150 ± 6	.04	b
Fasting glucose (mg/dL)	86 ± 1	91 ± 1	95 ± 1	<.0001	b
Glucose response (mg/dL · 3 h)	315 ± 5	337 ± 5	370 ± 6	NS	NS
Fasting insulin (μU/mL)	8.3 ± 0.3	10.4 ± 0.4	14.9 ± 0.7	<.0001	a, b
Insulin response (μU/mL · 3 h)†	120 ± 5	158 ± 9	234 ± 13	NS	NS

*Pairwise differences with $P < .05$, a: 1 *v* 2; b: 1 *v* 3; c: 2 *v* 3.

†Area under the curve in response to 75-g oral glucose challenge.

ship between BMI and insulin-mediated glucose disposal, the results permit comparison of the relative impact of variations in BMI and SSPG on the CVD risk factors measured. Thus, in Table 3, it is apparent that despite adjustment for differences in BMI, every CVD risk factor, with the exception of LDL-C concentration, increased progressively from the most insulin-sensitive (SSPG tertile 1) to the most insulin-resistant (SSPG tertile 3) group. In contrast, the results in Table 4 demonstrate that the effect of increasing BMI significantly contributed to LDL-C concentration among other CVD risk factors, but not to the plasma glucose and insulin responses to the oral glucose challenge and only minimally to TG concentration. Essentially similar conclusions as to the relationships between SSPG, BMI, and CVD risk markers were confirmed by multivariate analysis using BMI and SSPG as continuous variables.

It should also be noted that the magnitude of each CVD risk factor tended to increase progressively in parallel to SSPG tertile, whereas only a BMI above the first tertile was associated with increased CVD risk, ie, being in the third BMI tertile did not add significant excess risk compared with the second tertile. Thus, a mean BMI of 25 or greater was associated with increasing CVD risk, a cut-point that is congruent with the clinical classification system of the National Heart, Lung, and Blood Institute.[26]

In conclusion, these results demonstrate that while increased BMI is more prevalent in insulin-resistant individuals, not all overweight/obese persons are insulin resistant. Furthermore, because CVD risk factors were accentuated in association with increased degrees of insulin resistance, independently of BMI or age, it is the subset of overweight, obese individuals, who are also insulin resistant, who are at greatest CVD risk. Indeed, we have recently demonstrated that elevated levels of C-reactive protein are only increased in insulin-resistant, overweight individuals (*v* insulin-sensitive, equally-overweight individuals).[27] It is possible that the nature of the relationships described might have been somewhat different if we had been able to perform more sophisticated measures of regional body fat distribution in this large cohort. In addition, it must be emphasized that 77% of our population was of European ancestry, and the observed relationships between BMI and CVD risk may not apply to other ethnic groups. However, despite these caveats, we are unaware of any study that has examined the relationship between adiposity, a specific measure of insulin resistance obtained from a detailed physiologic assessment, and a series of metabolic CVD risk factors. Thus, we believe that these results provide support for the view that the most intensive efforts to decrease CVD risk should be directed towards those overweight individuals who are also insulin resistant.

Table 5. Prediction of CVD Risk Factors by SSPG and BMI Controlling for Age and Gender

CVD Risk Factor	R^2 for Model	SSPG (mg/dL)		BMI (kg/m^2)	
		Estimate ± SE (Standardized Estimate)	*P* Value	Estimate ± SE (Standardized Estimate)	*P* Value
SBP (mmHg)	0.27	0.05 ± 0.01 (0.18)	.0002	0.96 ± 0.25 (0.19)	.0001
DBP (mmHg)	0.24	0.05 ± 0.01 (0.31)	<.0001	0.36 ± 0.15 (0.12)	.02
LDL-C (mg/dL)	0.12	0.02 ± 0.03 (0.05)	NS	2.19 ± 0.48 (0.25)	<.0001
HDL-C (mg/dL)	0.30	−0.05 ± 0.01 (−0.28)	<.0001	−0.66 ± 0.16 (−0.20)	<.0001
Triglyceride (mg/dL)	0.31	0.39 ± 0.05 (0.41)	<.0001	2.72 ± 0.88 (0.15)	.002
Fasting glucose (mg/dL)	0.24	0.03 ± 0.01 (0.21)	<.0001	0.61 ± 0.14 (0.21)	<.0001
Glucose response (mg/dL)*	0.38	0.51 ± 0.04 (0.54)	<.0001	0.22 ± 0.81 (0.01)	NS
Fasting insulin (μU/mL)	0.40	0.04 ± 0.004 (0.47)	<.0001	0.43 ± 0.07 (0.25)	<.0001
Insulin response (μU/mL)*	0.43	1.04 ± 0.07 (0.61)	<.0001	2.38 ± 1.40 (0.07)	NS

*Area under the curve in response to 75-g oral glucose challenge.

REFERENCES

1. National Institutes of Health: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Obes Res 6(suppl 2):51S-209S, 1998
2. Kuczmarski RJ, Carroll MD, Flegal KM, et al: Varying body mass index cutoff points to describe overweight prevalence among U.S. adults: NHANES III (1988 to 1994). Obes Res 5:542-548, 1997
3. West KM, Kalbfleisch JM: Influence of nutritional factors on prevalence of diabetes. Diabetes 20:99-108, 1971
4. Havlik RJ, Hubert HB, Fabsitz RR, et al: Weight and hypertension. Ann Intern Med 98:855-854, 1983
5. Rimm EB, Stampfer MJ, Giovannucci E, et al: Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol 141:1117-1127, 1995
6. Olefsky JM, Reaven GM, Farquhar JW: Effects of weight reduction on obesity: Studies of carbohydrate and lipid metabolism. J Clin Invest 53:64-76, 1974
7. Ferrannini E, Natali A, Bell P, et al: Insulin resistance and hypersecretion in obesity. J Clin Invest 100:1166-1173, 1997
8. Warram JH, Martin BC, Krolewski AS, et al: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of the diabetic parents. Ann Intern Med 113:909-915, 1990
9. Lilloja S, Mott DM, Spraul M, et al: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. N Engl J Med 329:1988-1992, 1993
10. Depres JP, Lamarche B, Mauriege P, et al: Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 334:952-957, 1996
11. Yip J, Facchini FS, Reaven GM: Resistance to insulin-mediated glucose disposal as a predictor of cardiovascular disease. J Clin Endocrinol Metab 83:2773-2776, 1998
12. 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 48:989-994, 1999
13. Reaven, GM: Insulin resistance, compensatory hyperinsulinemia, and coronary heart disease: Syndrome X revisited, in Jefferson LS, Cherrington AD (eds): Handbook of Physiology, section 7, The Endocrine System, vol II, The Endocrine Pancreas and Regulation of Metabolism. New York, NY, Oxford University Press, 2001, pp 1169-1197
14. Golay A, Felber JP, Dusmet M, et al: Effect of weight loss on glucose disposal in obese and obese diabetic subjects. Int J Obes Relat Metab Disord 9:181-190, 1985
15. Weyer C, Hanson K, Bogardus C, et al: Long-term changes in insulin action and secretion associated with weight gain, loss, regain, and maintenance of body weight. Diabetologia 43:36-46, 2000
16. Galuska DA, Will JC, Serdula MK, et al: Are health care professionals advising obese patients to lose weight? JAMA 282:1576-1578, 1999
17. Wadden JA: Treatment of obesity by moderate and severe caloric restriction: Results of clinical trials. Ann Intern Med 119:688-693, 1993
18. American Diabetes Association: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 20:1183-1197, 1997
19. Jeppesen J, Facchini FS, Reaven GM: Individuals with high total cholesterol/HDL cholesterol ratios are insulin resistant. J Intern Med 243:293-298, 1998
20. Pei D, Jones CNO, Bhargava R, et al: Evaluation of octreotide to assess insulin-mediated glucose disposal by the insulin suppression test. Diabetologia 37:843-845, 1994
21. Shen S-W, Reaven GM, Farquhar JW: Comparison of impedance to insulin mediated glucose uptake in normal and diabetic subjects. J Clin Invest 49:2151-2160, 1970
22. Greenfield MS, Doberne L, Kraemer FB, et al: Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. Diabetes 30:387-392, 1981
23. Facchini FS, Hua N, Abbasi F, et al: Insulin resistance as a predictor of age-related diseases. J Clin Endocrinol Metab 86:3574-3578, 2001
24. Rexrode KM, Buring JE, Manson JE: Abdominal and total adiposity and risk of coronary heart disease in men. Int J Obes Relat Metab Disord 25:1047-1056, 2001
25. Han TS, Williams K, Sattar N, et al: Analysis of obesity and hyperinsulinemia in the development of metabolic syndrome: San Antonio Heart Study. Obes Res 10:923-931, 2002
26. NHLBI, NIH News Release: First Federal Obesity Clinical Guidelines Released. NIH1998
27. McLaughlin T, Abbasi F, Lamendola C, et al: Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 106:2908-2912, 2002