Insulin Resistance and Hyperinsulinemia

You can't have one without the other

SUN H. KIM, MD, MS
GERALD M. REAVEN, MD

OBJECTIVE — Recently, it has been suggested that insulin resistance and hyperinsulinemia can exist in isolation and have differential impacts on cardiovascular disease (CVD). To evaluate this suggestion, we assessed the degree of discordance between insulin sensitivity and insulin response in a healthy, nondiabetic population.

RESEARCH DESIGN AND METHODS — Insulin sensitivity was quantified by determining the steady-state plasma glucose (SSPG) concentration during an insulin suppression test in 446 individuals. The integrated insulin response was calculated after a 75-g oral glucose challenge. We analyzed the correlation between insulin resistance and insulin response in addition to quantifying the proportion in quartiles of insulin response by quartiles of insulin sensitivity. Then we compared CVD risk factors between individuals within the same insulin sensitivity quartile but within different insulin response quartiles to evaluate the differential clinical impact of insulin resistance and hyperinsulinemia.

RESULTS — Insulin resistance and insulin response were highly correlated ($r = 0.76$, $P < 0.001$). A majority (95%) of the most insulin-resistant individuals (top SSPG quartile) were either in the highest insulin response quartile (71%) or second highest (24%). Similarly, 92% of the most insulin-sensitive individuals (lowest SSPG quartile) were in the lowest two insulin response quartiles. There were minimal differences in CVD risk factors between individuals with different insulin responses but within the same insulin sensitivity quartile.

CONCLUSIONS — Although not perfectly related, insulin resistance and hyperinsulinemia rarely exist in isolation in a nondiabetic population. It is difficult to discern an independent impact of hyperinsulinemia on CVD risk factors associated with insulin resistance.

Diabetes Care **31:1433–1438, 2008**

In nondiabetic individuals, a hyperinsulinemic response to an oral glucose challenge is closely associated with decreases in insulin-mediated glucose uptake (1–3), as well as with a number of clinical syndromes associated with insulin resistance (4–10). However, the relationship is not perfect, and there have been several attempts to differentiate between the relative roles of insulin resistance and hyperinsulinemia in the development of clinical syndromes associated with these changes in insulin metabolism (11–14). For example, in a recent article, Ferrannini et al. (14) indicated in a large European population that only 60% of the most insulin-resistant individuals (bottom quartile of insulin sensitivity measured by the euglycemic insulin clamp) had the highest insulin response (top quartile) to an oral glucose challenge. These findings led to the suggestion that insulin resistance and hyperinsulinemia can be dissociated, exist in isolation from one another, and play different pathogenic roles in the genesis of the clinical syndromes associated with the two abnormalities. On the other hand, these authors did not address certain issues. Specifically, in their analyses they separated individuals into quartiles of insulin resistance and insulin response but did not provide information as to either the percentage of insulin-sensitive individuals in the highest quartile of insulin response or the percentage of insulin-sensitive individuals in the highest quartile of insulin response.

To better understand how discordant insulin resistance and hyperinsulinemia are, we quantified the percentage of individuals in quartiles of insulin response by quartiles of insulin sensitivity. In addition, to evaluate the differential clinical impact of insulin resistance and hyperinsulinemia, we compared cardiovascular disease (CVD) risk factors in individuals within the same quartile of insulin sensitivity but with differing insulin response levels.

RESEARCH DESIGN AND METHODS

Study subjects included 446 individuals who had participated in our research studies from 1990 to 1998 and who had given informed consent. All study protocols were approved by Stanford's Institutional Review Board. Individuals considered for inclusion were nondiabetic (15) and in good general health with no history of coronary artery, kidney, or liver disease. All individuals had the following procedures: measurement of height, weight, and systolic and diastolic blood pressures; lipid assessment; oral glucose tolerance test; and insulin suppression test to measure insulin sensitivity. Initially, 490 individuals were identified, but 44 were removed for missing data. We had published an article previously in which we described the distribution of insulin sensitivity in the entire population of 490 individuals, as well as the relationship between the quantitative estimate of insulin-mediated glucose disposal and several different surrogate estimates of this variable (16).

All metabolic testing was performed in Stanford's General Clinical Research Center after subjects fasted for 12 h. During the oral glucose tolerance test, plasma glucose and insulin were measured before (fasting) and 30, 60, 120, and 180 min after ingestion of 75 g of oral glucose (16). Individuals were classified as having impaired glucose tolerance (IGT) if their 2-h glucose value was between 7.8 and 11.1 mmol/l. Lipid measurements were performed by the core laboratory at Stanford and included total cholesterol, triglyceride, and HDL cholesterol concentrations.

From the Department of Medicine, Stanford University School of Medicine, Stanford, California.
Corresponding author: Sun H. Kim, sunhkim@stanford.edu.
Received 7 January 2008 and accepted 26 March 2008.
DOI: 10.2337/dc08-0045

Table 1—*Baseline characteristics of individuals by SSPG quartile*

	SSPG quartile 1: <4.8 mmol/l	SSPG quartile 2: 4.8–7.7 mmol/l	SSPG quartile 3: 7.8–11.7 mmol/l	SSPG quartile 4: >11.7 mmol/l	P_{trend}
n	112	111	112	111	
Age (years)	45 ± 12	48 ± 13	49 ± 14	52 ± 12	0.001
BMI (kg/m^2)	24 ± 3	25 ± 4	27 ± 4	30 ± 4	<0.001
Sex (% male)	46	48	41	52	0.53
Non-Hispanic white	92	88	83	86	0.12
IGT	2	5	13	38	<0.001
Insulin response (pmol · l^{-1} · 3 h^{-1})	570 (433–730)	780 (635–1,030)	1,093 (904–1,412)	1,991 (1,441–2,766)	<0.001
Fasting glucose (mmol/l)	4.8 ± 0.6	5.0 ± 0.6	5.1 ± 0.6	5.4 ± 0.7	<0.001
Fasting insulin (pmol/l)	49 (35–68)	63 (49–76)	76 (56–90)	118 (90–160)	<0.001
Total cholesterol (mmol/l)	4.6 ± 0.9	4.9 ± 0.9	4.8 ± 0.9	5.2 ± 0.9	<0.001
Triglyceride (mmol/l)	0.77 (0.60–0.99)	0.98 (0.79–1.39)	1.26 (0.87–1.65)	1.80 (1.38–2.42)	<0.001
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	1.1 ± 0.3	<0.001
LDL cholesterol (mmol/l)	2.8 ± 0.8	3.0 ± 0.8	3.0 ± 0.8	3.2 ± 0.8	0.001
Systolic blood pressure (mmHg)	120 ± 18	123 ± 18	127 ± 19	140 ± 20	<0.001
Diastolic blood pressure (mmHg)	72 ± 10	75 ± 11	78 ± 11	87 ± 11	<0.001

Data are means ± SD, median (interquartile range), or percent.

LDL cholesterol concentrations were calculated by the Friedewald formula.

Insulin sensitivity was measured directly with the modified version (17) of the insulin suppression test, initially introduced and validated by our research group (18). The values for insulin sensitivity obtained with this approach are highly correlated ($r > 0.9$) with the hyperinsulinemic-euglycemic clamp technique (19). In brief, after an overnight fast, an intravenous catheter was placed in each of the subject's arms. One arm was used for the administration of a 180-min infusion of octreotide (0.27 μg · m^{-2} · min^{-1}), insulin (32 mU · m^{-2} · min^{-1}), and glucose (267 mg · m^{-2} · min^{-1}); the other arm was used for collecting blood samples. Blood was drawn at 10-min intervals from 150 to 180 min of the infusion to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state insulin concentrations are similar in individuals, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, the higher the SSPG concentration, the more insulin resistant the individual is.

As there are no objective methods to classify individuals as insulin resistant or insulin sensitive, we divided individuals into quartiles of insulin sensitivity (SSPG concentration) to maintain consistency with the recent article by Ferrannini et al. (14). With this approach, a higher quartile indicates a greater degree of insulin resistance, i.e., quartile 4 contains the 25% most insulin-resistant individuals and quartile 1 contains the most insulin-sensitive individuals.

Insulin response was quantified by calculating the insulin area under the curve (over 3 h) by the trapezoidal method, and the subjects were again divided into quartiles based on the magnitude of their total integrated insulin response to glucose. Quartile 1 had the lowest insulin response, and quartile 4 had the highest response.

To evaluate the degree of concordance between insulin sensitivity and insulin response, we quantified the percentage of individuals in each of the four insulin response quartiles that were present within each of the four SSPG quartiles. In addition, in insulin-sensitive (SSPG quartile 1) and insulin-resistant individuals (SSPG quartile 4), we also compared CVD risk factors in those with different insulin response but within the same SSPG quartile to assess the independent impact of insulin on CVD risk factors.

Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). Triglyceride and insulin concentrations were log-transformed to obtain a more normal distribution for statistical tests; median and interquartile ranges are presented in the RESULTS. Trends in baseline characteristics among SSPG quartiles were analyzed using ANOVA for continuous measures and the Cochrane-Armitage test for proportions. Independent *t* tests were used to compare differences between the two groups.

RESULTS — Table 1 shows the demographic and metabolic characteristics of the individuals divided into quartiles of insulin sensitivity. Individuals in SSPG quartile 4 were somewhat older and heavier, but the groups were not different in terms of sex and ethnic distribution. As insulin resistance (SSPG) increased, the proportion of individuals with IGT increased. There was also a dramatic increase in the median insulin response, with the values in SSPG quartile 4 being 249% higher than those in SSPG quartile 1. Fasting plasma insulin concentrations also increased in parallel with degree of insulin resistance. In addition, the interquartile ranges did not overlap between these two extreme groups. Finally, the more insulin resistant the group was, the more unfavorable the CVD risk profile was. Thus, individuals in SSPG quartile 4 had higher blood pressures, and all components of the lipid panel also increased or, in the case of HDL cholesterol, decreased.

The results in Fig. 1*A* demonstrate that the relationship between insulin resistance (SSPG) and insulin response was best expressed by an exponential function ($r = 0.76$, $P < 0.001$) with no difference by sex (male, $r = 0.77$; female, $r = 0.76$). When insulin response was log-transformed, the relationship between in-

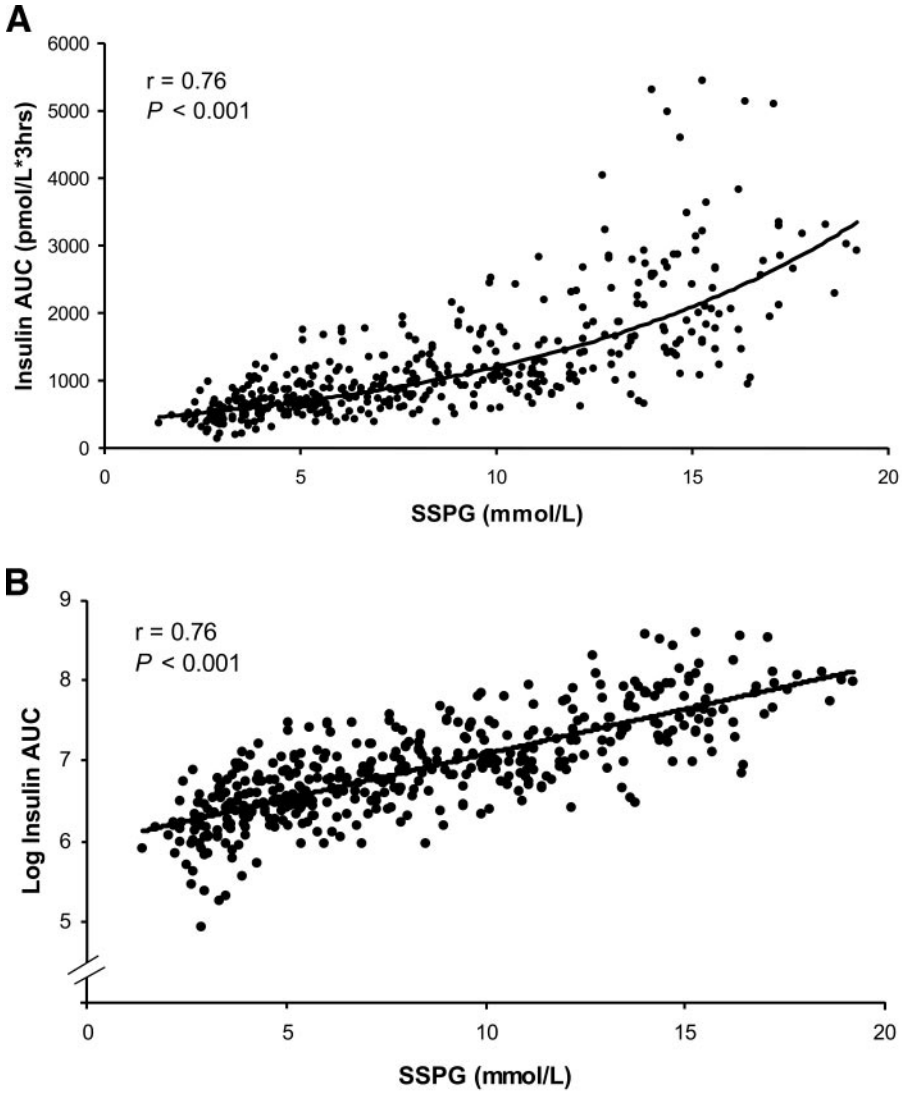

Figure 1—*Relationship between insulin resistance (SSPG) and insulin response was best expressed as an exponential function* (A) *or a linear function when insulin response (insulin AUC) was log-transformed* (B).

sulin resistance and insulin response was equally well represented by a linear function ($r = 0.76$, $P < 0.001$) (Fig. 1*B*). This relationship was stronger than that between SSPG and fasting insulin ($r = 0.61$), 2-hour insulin ($r = 0.70$), and 2-hour integrated insulin response ($r = 0.74$) ($t > 4$ for all comparisons, degrees of freedom 443, $P < 0.001$). The strong relationship between SSPG and insulin response remained even when individuals with IGT were excluded ($r = 0.74$, $P < 0.001$, $n = 381$).

The close relationship between insulin resistance and insulin response is also highlighted in Table 2, which shows the proportion of individuals in each of the four SSPG quartiles as a function of their insulin response quartile. In the most insulin-sensitive quartile (SSPG quartile 1), 64% had the lowest insulin response (quartile 1) and 28% had the second lowest insulin response (quartile 2), with a total of 92% in the bottom two insulin response quartiles. No one was in the highest insulin response quartile (quartile 4). In the most insulin-resistant quartile (SSPG quartile 4), 71% were in the highest insulin-response quartile (quartile 4) and 24% were in the second highest (quartile 3), with a total of 95% in the top two quartiles. Only 1% was in the lowest insulin response quartile. Excluding individuals with IGT did not substantially change these findings, i.e., 92% of individuals in the two most insulin-resistant quartiles were in the two quartiles with the highest insulin response, and only 1% of insulin-resistant individuals were in the lowest insulin response quartile.

The data in Table 2 emphasize that there were relatively few insulin-sensitive individuals (SSPG quartile 1) whose insulin responses were in the two highest quartiles (8%) and very few insulin-resistant individuals (SSPG quartile 4) with insulin responses in the two lowest quartiles (5%). Therefore, to further pursue the relationship between degree of insulin sensitivity, magnitude of insulin response, and CVD risk, we compared differences in CVD risk factors between those with the lowest insulin responses (quartiles 1 and 2) within the most insulin-sensitive quartile (SSPG quartile 1), as well as between individuals with the two highest insulin responses (quartiles 3 and 4) within the most insulin-resistant quartile (SSPG quartile 4) (Table 3).

Focusing first on insulin-sensitive individuals (SSPG quartile 1), by selection, insulin response was statistically different in the two insulin response groups. In addition, SSPG concentration was significantly higher in individuals with the greater insulin response (insulin response quartile 2 versus quartile 1) despite being within the same insulin sensitivity quartile. Finally, there were also marginally higher concentrations of fasting insulin,

Table 2—*Proportion of individuals in insulin response quartiles by SSPG quartiles*

Insulin response	SSPG quartile 1	SSPG quartile 2	SSPG quartile 3	SSPG quartile 4
n	112	111	112	111
Quartile 1: <648 (pmol · l^{-1} · 3 h^{-1})	64	27	8	1
Quartile 2: 648–969 (pmol · l^{-1} · 3 h^{-1})	28	44	24	4
Quartile 3: 970–1,514 (pmol · l^{-1} · 3 h^{-1})	8	20	48	24
Quartile 4: >1,514 (pmol · l^{-1} · 3 h^{-1})	0	9	20	71

Table 3—*Comparison of cardiovascular risk factors in individuals with different insulin responses but within the same insulin sensitivity quartile*

	SSPG quartile 1: insulin sensitive			SSPG quartile 4: insulin resistant		
	Insulin response quartile 1	Insulin response quartile 2	*P* value	Insulin response quartile 3	Insulin response quartile 4	*P* value
n	72	31		27	79	
Insulin response ($pmol \cdot l^{-1} \cdot 3\ h^{-1}$)	484 (390–552)	738 (689–853)	<0.001	1,233 (1,075–1,422)	2,441 (1,870–2,931)	<0.001
SSPG (mmol/l)	3.3 ± 0.8	3.8 ± 0.7	0.004	13.5 ± 1.5	14.8 ± 1.7	0.001
Age (years)	45 ± 12	46 ± 11	0.93	49 ± 14	53 ± 11	0.24
Sex (% male)	46	45	0.95	59	51	0.44
Non-Hispanic white	92	94	0.74	89	86	0.71
BMI (kg/m^2)	23 ± 3	24 ± 3	0.47	29 ± 5	31 ± 4	0.07
Fasting glucose (mmol/l)	4.8 ± 0.6	4.9 ± 0.4	0.34	5.4 ± 0.8	5.5 ± 0.6	0.65
Fasting insulin (pmol/l)	42 (35–56)	56 (42–69)	0.08	97 (76–111)	132 (104–181)	<0.001
Total cholesterol (mmol/l)	4.5 ± 0.7	4.8 ± 1.0	0.08	5.2 ± 0.9	5.2 ± 0.9	0.78
Triglyceride (mmol/l)	0.75 (0.60–0.92)	0.93 (0.67–1.10)	0.08	1.75 (1.25–2.25)	1.81 (1.41–2.46)	0.18
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.4 ± 0.4	0.75	1.3 ± 0.3	1.1 ± 0.2	<0.001
LDL cholesterol (mmol/l)	2.7 ± 0.7	3.0 ± 1.0	0.12	3.1 ± 0.8	3.2 ± 0.8	0.73
Systolic blood pressure (mmHg)	122 ± 19	117 ± 16	0.21	143 ± 23	140 ± 19	0.52
Diastolic blood pressure (mmHg)	72 ± 10	74 ± 10	0.33	88 ± 12	86 ± 11	0.54

Data are means ± SD, median (interquartile range), or percent.

total cholesterol, and triglyceride (all $P = 0.08$) in the higher insulin response quartile (quartile 2).

In the insulin-resistant group (SSPG quartile 4), as above, the insulin responses were significantly different by selection. Those individuals with the higher insulin response (insulin response quartile 4 versus 3) also had higher SSPG and fasting insulin concentrations and a lower HDL cholesterol concentration.

We also repeated our major analyses with the inclusion criteria used in a recent article addressing the same issue (14): age 30–60 years, arterial blood pressure <140/90 mmHg, total serum cholesterol <7.8 mmol/l, and serum triglycerides <4.6 mmol/l. This decreased our study population to 227. The relationship between SSPG and insulin response (log-transformed) remained similar ($r = 0.78$, $P < 0.001$). Within the top insulin-resistant quartile, 63% were in insulin response quartile 4 and 30% were in insulin response quartile 3, with a total of 93% in the top two insulin response quartiles.

CONCLUSIONS — In this study of nondiabetic individuals, we identified a highly significant correlation between insulin resistance and insulin response ($r = 0.76$), indicating that the relationship between these two variables is a close one. In this context, it should be recognized that the plasma insulin response to an oral glucose challenge will vary as a function of the interplay between several biological systems, including, at a minimum, degree of insulin resistance, insulin secretory function, plasma glucose concentration, and insulin removal rate from plasma. The relationship between insulin resistance and insulin response is further compounded by the inherent error in making either measurement. We have previously shown that SSPG concentration, when measured twice in the same individual, varied by 10–30% in ~25% of those studied (19), and the plasma insulin concentration 2 h after a 75-g oral glucose load varied by >20% in two-thirds of the individuals studied when repeat measurements were made 2 days apart (20). In view of these considerations, the fact that the relationship between insulin resistance and insulin response is not a perfect one is hardly surprising. Indeed, we would argue that what is surprising is how strong the relationship seems to be ($r = 0.76$) and how rare (5%) it is to find insulin-resistant individuals (SSPG quartile 4) who have an insulin response below the median for this population or insulin-sensitive (SSPG quartile 1) individuals who have an insulin response above the median (8%).

Given the results of this analysis, it is difficult to ignore the possibility that insulin resistance and hyperinsulinemia tightly coexist. However, a recent study in a European population challenged the degree of association between these two variables (14). Although these authors found insulin sensitivity and insulin response to be closely associated (Spearman's rank correlation = −0.63 in men and −0.50 in women), they argued that each could be found in isolation in the population. This conclusion was based on the fact that only 60% of the individuals in the most insulin-resistant quartile were also in the highest insulin response quartile. However, no information was provided regarding the proportion in the other insulin response quartiles. As can be seen in Table 2, the distribution of insulin response is not evenly dispersed within the top insulin-resistant quartile (SSPG quartile 4) but is skewed to the top two insulin response quartiles. Certainly, 100% of the most insulin-resistant individuals are not in the top insulin response quartile, but 95% are in the top two quartiles. The same can be said in reverse: although not all insulin-sensitive individuals (SSPG quartile 1) are in the lowest insulin response quartile (64%), 92% are in the lowest two quartiles.

It is difficult to compare our results to those of the European cohort, as they did not assess the distribution of insulin response in the same manner. Furthermore, our populations seem to be somewhat different. We had more individuals who were in both the highest insulin-resistance and highest insulin-response quartiles than the European study did (71 vs. 60%). In addition, the *r* value between

insulin sensitivity and insulin response was higher in our study. On the other hand, when inclusion criteria similar to those in the European study were used, we had similar proportions of individuals in both the top insulin resistance and insulin response quartiles (63%). However, the total in the top two insulin response quartiles stayed high (93%). In addition, the *r* value remained at 0.78 between insulin sensitivity and insulin response.

Although the degree of insulin resistance contributes strongly to insulin response, we understand that many factors affect the variance in insulin response as discussed above. Another factor is obesity, which increases insulin response by enhancing insulin secretion (21–23) and decreasing insulin clearance (24,25), especially in insulin-resistant individuals (4). This instance can be seen in this study when individuals with higher insulin response tended to be more obese than others, even within the same SSPG quartile (Table 3), a finding that was most evident in the top insulin-resistant quartile (SSPG quartile 4). On the other hand, even in this instance, insulin resistance is also higher in the individuals with higher insulin response. Therefore, it is again difficult to separate insulin response from insulin sensitivity.

Because of this collinearity, it is difficult to define the putative effects of insulin resistance versus compensatory hyperinsulinemia on CVD risk factors, and the data in Table 3 illustrate this point. In the most insulin-sensitive quartile (SSPG quartile 1), when we compared CVD risk factors in those in the lowest insulin response quartile to those of individuals in the next highest insulin response quartile, the two groups differed only in degree of insulin resistance. Similarly, in the most insulin-resistant quartile (SSPG quartile 4), SSPG concentrations were higher in those with the greatest insulin response (quartile 4) compared with those in insulin response quartile 3. However, other than a lower HDL cholesterol concentration in those with the higher insulin response, there were no significant differences in CVD risk factors between the two insulin response groups. These data do not support a role of hyperinsulinemia, independent of insulin resistance, in the development of known CVD risk factors. It should also be noted that even in the European cohort discussed above, insulin resistance clustered with higher insulin response, higher triglycerides, and lower HDL cholesterol during factor analysis.

In summary, insulin resistance and hyperinsulinemia are closely linked. Although insulin sensitivity does not account for 100% of the variance in insulin response, it is difficult to discern an independent impact of hyperinsulinemia on CVD risk factors associated with insulin resistance (26). Perhaps the simplest pathophysiological approach is to view insulin resistance/compensatory hyperinsulinemia as one entity in nondiabetic individuals, rather than attempting by statistical methods to come to conclusions as to which abnormality is caused by insulin resistance and which is caused by hyperinsulinemia.

Acknowledgments— This research was supported by the National Institutes of Health (General Clinical Research Center grants RR-00070 and K23 MH079114 to S.H.K.).

Parts of this study were presented in abstract form at the 68th meeting of the American Diabetes Association, San Francisco, California, 6–10 June 2008.

References

1. Reaven GM, Olefsky JM: Relationship between heterogeneity of insulin responses and insulin resistance in normal subjects and patients with chemical diabetes. *Diabetologia* 13:201–206, 1977
2. Hollenbeck C, Reaven GM: Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. *J Clin Endocrinol Metab* 64: 1169–1173, 1987
3. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
4. Kim SH, Abbasi F, Reaven GM: Impact of degree of obesity on surrogate estimates of insulin resistance. *Diabetes Care* 27: 1998–2002, 2004
5. Welborn TA, Breckenridge A, Rubinstein AH, Dollery CT, Fraser TR: Serum-insulin in essential hypertension and in peripheral vascular disease. *Lancet* 1:1336–1337, 1966
6. Pyorala K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care* 2:131–141, 1979
7. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH: Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. *Lancet* 1:1356–1359, 1989
8. 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
9. Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, Karim R, Lin R, Samarasinghe D, Liddle C, Weltman M, George J: NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 35:373–379, 2002
10. Dunaif A, Segal KR, Futterweit W, Dobrjansky A: Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 38: 1165–1174, 1989
11. Lind L, Lithell H, Pollare T: Is it hyperinsulinemia or insulin resistance that is related to hypertension and other metabolic cardiovascular risk factors? *J Hypertens* 11 (Suppl.):S11–S16, 1993
12. Weyer C, Hanson RL, Tataranni PA, Bogardus C, Pratley RE: A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance: evidence for a pathogenic role of relative hyperinsulinemia. *Diabetes* 49: 2094–2101, 2000
13. Ferrannini E, Balkau B: Insulin: in search of a syndrome. *Diabet Med* 19:724–729, 2002
14. Ferrannini E, Balkau B, Coppack SW, Dekker JM, Mari A, Nolan J, Walker M, Natali A, Beck-Nielsen H: Insulin resistance, insulin response, and obesity as indicators of metabolic risk. *J Clin Endocrinol Metab* 92:2885–2892, 2007
15. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
16. Yeni-Komshian H, Carantoni M, Abbasi F, Reaven GM: Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. *Diabetes Care* 23: 171–175, 2000
17. Pei D, Jones CN, Bhargava R, Chen YD, Reaven GM: Evaluation of octreotide to assess insulin-mediated glucose disposal by the insulin suppression test. *Diabetologia* 37:843–845, 1994
18. Shen SW, Reaven GM, Farquhar JW: Comparison of impedance to insulin-mediated glucose uptake in normal subjects and in subjects with latent diabetes. *J Clin Invest* 49:2151–2160, 1970
19. Greenfield MS, Doberne L, Kraemer F, Tobey T, Reaven G: Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. *Diabetes* 30:387–392, 1981
20. Olefsky JM, Reaven GM: Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. *Diabetes* 23:449–453, 1974
21. Elahi D, Nagulesparan M, Hershcopf RJ,

Muller DC, Tobin JD, Blix PM, Rubenstein AH, Unger RH, Andres R: Feedback inhibition of insulin secretion by insulin: relation to the hyperinsulinemia of obesity. *N Engl J Med* 306:1196–1202, 1982
22. Bonora E, Zavaroni I, Bruschi F, Alpi O, Pezzarossa A, Guerra L, Dall'Aglio E, Coscelli C, Butturini U: Peripheral hyperinsulinemia of simple obesity: pancreatic hypersecretion or impaired insulin metabolism? *J Clin Endocrinol Metab* 59: 1121–1127, 1984
23. Polonsky KS, Given BD, Hirsch L, Shapiro ET, Tillil H, Beebe C, Galloway JA, Frank BH, Karrison T, Van Cauter E: Quantitative study of insulin secretion and clearance in normal and obese subjects. *J Clin Invest* 81:435–441, 1988
24. Jones CN, Abbasi F, Carantoni M, Polonsky KS, Reaven GM: Roles of insulin resistance and obesity in regulation of plasma insulin concentrations. *Am J Physiol* 278:E501–E508, 2000
25. Meistas MT, Margolis S, Kowarski AA: Hyperinsulinemia of obesity is due to decreased clearance of insulin. *Am J Physiol* 245:E155–E159, 1983
26. Reaven GM: The insulin resistance syndrome. *Curr Atheroscler Rep* 5:364–371, 2003