Insulin Resistance and Hyperinsulinemia

You can’t have one without the other

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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.

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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 whether the percentage of insulin-resistant individuals in the lowest 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.

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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 | \( P_{\text{trend}} \) |
|-----------------------------|---------------------------------|---------------------------------|-------------------------------|------------------|
| \( \text{n} \)              | 112                             | 111                             | 112                           | 111              |
| Age (years)                 | 45 ± 12                         | 48 ± 13                         | 49 ± 14                       | 52 ± 12          | 0.001 |
| BMI (kg/m²)                 | 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  |
| T2DM                        | 2                               | 5                               | 13                            | 38               | <0.001 |
| Insulin response (pmol·l⁻¹·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 \((0.27 \, \mu@g \cdot m^{-2} \cdot min^{-1})\), insulin \((32 \, mU \cdot m^{-2} \cdot min^{-1})\), and glucose \((267 \, mg \cdot m^{-2} \cdot min^{-1})\); 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, 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-
Insulin resistance and insulin response was equally well represented by a linear function (\( r = 0.76, P < 0.001 \)) (Fig. 1B). 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,

![Figure 1](image1.png)

**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).

| Insulin response | SSPG quartile 1 | SSPG quartile 2 | SSPG quartile 3 | SSPG quartile 4 |
|------------------|----------------|----------------|----------------|----------------|
| \( n \)           | 112            | 111            | 112            | 111            |
| Quartile 1: <648 (pmol \cdot l^{-1} \cdot 3 \cdot h^{-1}) | 64 | 27 | 8 | 1 |
| Quartile 2: 648–969 (pmol \cdot l^{-1} \cdot 3 \cdot h^{-1}) | 28 | 44 | 24 | 4 |
| Quartile 3: 970–1,514 (pmol \cdot l^{-1} \cdot 3 \cdot h^{-1}) | 8 | 20 | 48 | 24 |
| Quartile 4: >1,514 (pmol \cdot l^{-1} \cdot 3 \cdot h^{-1}) | 0 | 9 | 20 | 71 |
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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        | Insulin response quartile 3 | Insulin response quartile 4 |
| n              | 72                                | 31                                | 27                          | 79                          |
| Insulin response (pmol·l⁻¹·h⁻¹·3 h⁻¹) | 484 (390–552)                     | 738 (689–853)                     | 1,233 (1,075–1,422)         | 2,441 (1,870–2,931)         |
| SSPG (mmol/l)  | 3.3 ± 0.8                         | 3.8 ± 0.7                         | 13.5 ± 1.5                  | 14.8 ± 1.7                  |
| Age (years)    | 45 ± 12                           | 46 ± 11                           | 49 ± 14                     | 53 ± 11                     |
| Sex (% male)   | 46                                | 45                                | 59                          | 51                          |
| Non-Hispanic white | 92                               | 94                               | 89                          | 86                          |
| BMI (kg/m²)    | 23 ± 3                            | 24 ± 3                            | 29 ± 5                      | 31 ± 4                      |
| Fasting glucose (mmol/l) | 4.8 ± 0.6                        | 4.9 ± 0.4                         | 5.4 ± 0.8                   | 5.5 ± 0.6                   |
| Fasting insulin (pmol/l) | 42 (35–56)                       | 56 (42–69)                        | 97 (76–111)                 | 132 (104–181)               |
| Total cholesterol (mmol/l) | 4.5 ± 0.7                         | 4.8 ± 1.0                         | 5.2 ± 0.9                   | 5.2 ± 0.9                   |
| Triglyceride (mmol/l) | 0.75 (0.60–0.92)                 | 0.93 (0.67–1.10)                  | 1.75 (1.25–2.25)            | 1.81 (1.41–2.46)            |
| HDL cholesterol (mmol/l) | 1.5 ± 0.4                         | 1.4 ± 0.4                         | 1.3 ± 0.3                   | 1.1 ± 0.2                   |
| LDL cholesterol (mmol/l) | 2.7 ± 0.7                         | 3.0 ± 1.0                         | 3.1 ± 0.8                   | 3.2 ± 0.8                   |
| Systolic blood pressure (mmHg) | 122 ± 19                         | 117 ± 16                         | 143 ± 23                    | 140 ± 19                    |
| Diastolic blood pressure (mmHg) | 72 ± 10                          | 74 ± 10                           | 88 ± 12                     | 86 ± 11                     |

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

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 not perfectly 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, in both the top insulin resistance and insulin response quartile, the two groups differed only in degree of insulin resistance. At least 10% 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.

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