Temporal Relations between Obesity and Insulin: Longitudinal Data from the Normative Aging Study

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Although obesity and insulin levels are generally associated in cross-sectional data, the temporal and causal nature of their association is not yet clear. Increased obesity may have preceded increased insulin levels or vice versa. The authors examined the temporal relations between fasting insulin blood levels and weight in longitudinal data from the ongoing Normative Aging Study. Two insulin measurements from which a rate of change (ΔInsulin) could be calculated were available from 376 non-diabetic male subjects (mean age = 62.1 years). Rates of change in weight could be calculated for the previous inter-examination period (ΔWeight1), the contemporaneous period (ΔWeight2), and the inter-examination period following the second insulin measurement (ΔWeight3). ΔWeight2 was a significant predictor (p = 0.0005) of ΔInsulin in multiple linear regression models that included control for potential confounders (body mass index, waist-to-hip ratio, antihypertensive and diuretic medication use, and age) and for correlation between the initial level and change in insulin (mean fasting insulin). ΔWeight1 was added to the model and was found not to be statistically significant (p = 0.15). When the model was stratified by age tertile, the regression coefficient on ΔWeight1 was -0.44 (p = 0.018) for the youngest stratum, -0.06 (p = 0.72) for the middle stratum, and 0.21 (p = 0.19) for the oldest men. Similarly, ΔInsulin was a significant predictor of ΔWeight3 (p = 0.026) in a separate regression model. These findings are consistent with both possible temporal sequences of association between changes in insulin and obesity. The intricate homeostatic mechanisms that regulate changes in insulin and obesity may not be readily amenable to description in terms of cause and effect. Am J Epidemiol 1998;147:173-9.

causality; diabetes mellitus, non-insulin-dependent; insulin; insulin resistance; obesity; risk factors

Obesity is recognized as a major preventable risk factor that contributes to a broad range of common chronic diseases in the United States, including hypertension, cardiovascular disease, and diabetes mellitus. Increased risk of insulin-resistant states, including glucose intolerance (1, 2) and non-insulin-dependent diabetes mellitus (NIDDM) in obese subjects (1), has also been well documented. However, the nature of the relation between insulin levels, insulin resistance, and obesity is not yet clear (3).

A positive correlation between fasting insulin levels (an index of relative insulin resistance) and obesity, particularly the central or android pattern (4, 5), has been reported from cross-sectional data. Centrally obese individuals tend to have higher fasting insulin levels and greater levels of insulin resistance (6). Given that such an association exists, there may either be a causal relation or an as-yet-undetected common cause. If a causal relation exists, it might go in either direction, i.e., obesity may cause increased levels of fasting insulin, or increased insulin levels might lead to obesity.

From a physiologic perspective, a number of plausible mechanisms by which increased mass of adipose tissue might contribute to defective insulin action, and thus to compensatory increases in levels of circulating insulin, have been proposed (3, 7). On the other hand, a theoretical mechanism by which insulin resistance might lead to carbohydrate craving (8) and thus to weight gain has been suggested. Evidence from controlled trials (9) and from clinical data (10) that exog-
MATERIALS AND METHODS

The Normative Aging Study is an ongoing longitudinal study that was established by the Veterans Administration in 1961. Details of the study protocol have been described in detail (11). Briefly, the study cohort comprised 2,280 community-dwelling men from the Boston area, recruited over 9 years from April 1961. Volunteers were aged 21–80 years at study entry and were screened according to specific clinical, laboratory, radiologic, electrocardiographic, and medical history criteria (11), so that all participants were free of chronic medical conditions at entry.

Measurements

Each participant reports for a periodic examination comprising a uniform medical history questionnaire and physical examination in addition to blood and urine tests. Subjects fast overnight before their examination. During the period from February 1987 until July 1991, serum insulin levels from fasting blood samples were determined using a solid-phase iodine-125 radioimmunoassay (Coat-A-Count Insulin 1987, Diagnostic Products Corp., Los Angeles, California). The intraassay and interassay coefficients of variation were 3–5 percent and 5–7 percent, respectively. The first recorded fasting insulin value was taken as the baseline (first insulin) and age was calculated in years at the visit when this first insulin measurement was recorded. Anthropometric measures were taken with the subject wearing undershorts and socks only. Height was measured against a wall chart with the subject standing erect, with feet together. Weight was measured on a beam scale to the nearest 0.5 lb and converted to kg.

The circumference of the abdomen at the level of the umbilicus measured without compression of the skin was recorded as the waist circumference. The circumference at the level of the greatest protuberance of the buttocks measured without compression of the skin was recorded as the hip circumference. The ratio of the waist circumference to the hip circumference (WHR) was used as an indicator of fat distribution, with higher values suggesting a more central pattern.

Body mass index (BMI) (weight (kg)/height (m)^2) was used as a measure of relative adiposity.

Rates of change

In order to detect change in fasting insulin blood levels, subjects with insulin measurements at two successive examinations were selected. Of these, subjects who were known to have ever taken oral hypoglycemic agents or to have injected insulin were excluded from further analysis. The rate of change in fasting insulin levels over the interval between examinations (∆Insulin) was estimated as the difference between the last and the first levels divided by the interval duration in years, giving a slope in µIU/year.

Change in body weight was used as an indicator of change in obesity, because only minor changes in height and muscle mass were thought likely to occur over the study period. Rates of change for body weight were calculated as the difference between the last and first weights in a given period, divided by the duration of the interval, giving a slope in g/year. Weight slopes were calculated for the inter-examination interval preceding the first insulin measurement (∆Weight1), the interval between the two insulin measurements (∆Weight2), and the interval following the last insulin measurement (∆Weight3). The estimation of slopes from values from the four examinations used in this study is illustrated in figure 1, where the estimation of ∆Insulin from first insulin, second insulin, and the interval between examinations is illustrated for one hypothetical case. Note that, in practice, the interval between successive examinations was not fixed for any individual. The mean interval in years between successive examinations was 3.7, 3.3, and 3.0 for the four Normative Aging Study examinations for the subjects included in this study.

Exclusions

In the interval during which insulin measurements were being made, a total of 1,223 subjects had fasting serum insulin levels measured on one or more occasions. A total of 395 subjects were examined twice during this interval and so had two fasting insulin measurements available. Only these subjects were considered for inclusion, because the hypotheses being explored concerned changes in insulin levels. Eighteen of these potential subjects were excluded because they...
had been prescribed antidiabetic medication (insulin or oral hypoglycemic agents) at any time during the study period. These excluded subjects had higher mean fasting insulin levels (24.6 μIU/ml vs. 9.6 μIU/ml, p = 0.05), higher WHR (1.01 vs. 0.98, p = 0.03), higher BMI (28.7 vs. 26.9, p = 0.02), and lower ΔWeight1 (mean loss of 604 g/year vs. mean gain of 158 g/year, p = 0.008), but there were no significant differences in age, weight, ΔWeight2, ΔWeight3, or ΔInsulin.

One of the remaining 377 subjects was excluded from the analysis as a physiologically implausible outlier, because their second fasting insulin level was found to be more than five standard deviations above the mean. This level seemed very unlikely in the presence of a fasting glucose value well within normal limits and no recorded diagnosis or treatment for diabetes mellitus.

The records of 14 of the 376 remaining eligible subjects indicated that they were of African-American descent. There were no differences by t test for any of the study variables between these subjects and the other 362 whites, and repeating all the analyses after excluding this small group made no substantial difference to the findings, so they were included in the study.

Analysis

All analyses were performed using version 6.11 of the Statistical Analysis System (SAS) package (12). Multiple linear regression was used to model the relations between ΔInsulin and ΔWeight. A substantial proportion of hypertensives are obese and insulin resistant (13) and, in particular, the use of thiazide diuretics is thought to lead to increased levels of insulin resistance (14), so binary indicator terms for use of any antihypertensive medication and for use of thiazide diuretics were added to all regression models. Other potential confounders, including age, BMI, and WHR, were also added to all models. Bias due to correlation between the initial level and rate of change (15) was controlled by including the average of the two values used to estimate the rate of change of the dependent variable in all models. In practice, use of the mean rather than the first value made relatively little difference to the results (not shown).

In the first model, the contemporaneous relation between ΔInsulin and ΔWeight2 was modeled by regressing ΔInsulin on ΔWeight2 with control for potential confounders and mean fasting insulin to control for regression to the mean. Exploration of the relation between concurrent changes in weight and insulin levels did not directly assist in determining the temporal relation, but if ΔWeight2 and ΔInsulin were associated with each other, adjustment for confounding from ΔWeight2 would be needed in models exploring the temporal association between weight and insulin changes.

In order to test the hypothesis that change in weight in the preceding period predicted change in insulin levels, ΔWeight1 was added to the first model. This second regression model was tested for all subjects combined and then within strata defined by tertile of age to test for effect modification.

Finally, to test the hypothesis that change in insulin level predicted change in weight during the following inter-examination period, ΔWeight3 was regressed on
ΔInsulin with control for potential confounders in the third model. The mean of the two weight values used to calculate ΔWeight3 was included in this third model to control for correlation between the initial level and change in weight.

RESULTS

Data for the 376 eligible subjects are summarized in table 1. The slope on insulin was positive and significantly different from zero. The first two weight slopes were positive, while the third was not significantly different from zero.

Spearman correlation coefficients between the major variables of interest are shown in table 2. Age was significantly negatively correlated with weight, with the two weight slopes of interest, and with BMI. The weight recorded at the same time as the first insulin measurement was positively correlated with that insulin level as well as with WHR, BMI, and the slope on weight during the period before the first insulin measurement was taken. The negative correlation between the first insulin level and ΔInsulin suggests that there was regression to the mean, where subjects with high first insulin levels were likely to have low second levels, giving a low or negative ΔInsulin.

In exploring the extent to which change in insulin level (ΔInsulin) was predictive of change in concurrent weight slope (ΔWeight2), the only confounder associated with ΔInsulin in these data was first insulin (table 2). Results from the first regression model are shown in table 3. An association between rising fasting insulin levels and weight gain is suggested because the coefficient on ΔWeight2 is positive and significantly different from zero.

Table 4 shows the results from the second model, in which ΔWeight1 was added to the first model shown in table 3, for all subjects combined and by age tertile stratum. The coefficient on ΔWeight1 was not significantly different from zero for all subjects combined. In exploring the data, it was noted that the coefficient was negative for the youngest stratum, negative (non-significant) for the middle stratum, and positive (non-significant) for the oldest stratum, suggesting that age was an effect modifier in the relation. The smaller number of subjects in each stratum decreased the statistical power to detect a true effect, and this finding was not the result of any a priori hypotheses.

Results from the third model, regressing ΔWeight3 on ΔInsulin are shown in table 5. The term on ΔInsulin was positive, suggesting that an increase in fasting insulin was associated with weight gain during the inter-examination period that followed the second insulin measurement.

DISCUSSION

A significant positive association between concurrent increases in body weight and increasing fasting insulin levels was found in this sample. No causal relation can be inferred from this observation, because the temporal sequence of events cannot be determined. However, in exploring the temporal relation between changes in fasting blood insulin level and changes in body weight, evidence for both of the possible temporal sequences was found.

Limitations

The data reported here were observational. Although experimental data would give stronger evidence about causality, there are substantial ethical problems in allocation to an intervention designed to induce weight gain, while the design of an intervention to lower serum insulin without other metabolic alteration represents a substantial practical challenge.

The Normative Aging Study cohort comprised middle-aged to elderly males. The extent to which these findings are generalizable to females or to younger adults is not known because patterns of change in weight, fat distribution, and associated neuroendocrine disturbances vary with age and sex (6). To date, no comparable data have been reported from more generalizable cohorts. Although repeated measurements of body weight are available from many cohorts, repeated measures of insulin are not often made.

The ideal interval between weight and insulin measurements for detecting a temporal relation is not known, because the time course of changes in one leading to changes in the other is not known. The data reported here suggest that changes may be observed over several years, but it is possible that stronger
The use of change in body weight as a measure of change in obesity assumes that the major source of anthropometric values available for epidemiologic use (16). Generally among the most reliable and precise anthropometric values available for epidemiologic use (16). The use of change in body weight as a measure of change in obesity assumes that the major source of associations might be seen with more finely spaced observations.

Changes in body weight were used in this study as an indicator of change in obesity. Body weight is generally among the most reliable and precise anthropometric values available for epidemiologic use (16). The use of change in body weight as a measure of change in obesity assumes that the major source of weight fluctuation in these adult men was body fat. Decreases in lean body mass may also occur, particularly in chronic systemic illness and cachexia, but increased lean body mass is an unlikely cause of weight gain in older males. The other likely source of weight fluctuation, particularly in the short term, is altered fluid balance. Although the Normative Aging Study subjects were initially disease free, three decades later, a substantial proportion of the sample studied here (21 percent) had diuretic medication prescribed as part of their medical management during the time period covered by this study. Weight fluctuation may result from changed or irregular diuretic dosage and thus diuretic use might be a source of bias in this study, but this could not be readily quantified.

Fasting insulin level has been recommended for epidemiologic studies (17) as the best choice for a practicable indicator of relative insulin resistance, because it was highly correlated with the results of hyperinsulinemic euglycemic clamp studies in relatively large samples of normal and glucose intolerant subjects. The assay used for insulin in this study was nonspecific, and cross-reaction with proinsulin would be expected. However, we are not aware of any assay

**TABLE 2.** Spearman rank correlations between continuous variables, Normative Aging Study, 1987–1991

<table>
<thead>
<tr>
<th>Regression term</th>
<th>Coefficient</th>
<th>Standardized coefficient</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.08</td>
<td>-</td>
<td>0.39</td>
</tr>
<tr>
<td>ΔWeight2 (g/year)</td>
<td>0.35</td>
<td>0.18</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.022</td>
<td>0.0082</td>
<td>0.88</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.081</td>
<td>-0.14</td>
<td>0.038</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>-0.90</td>
<td>-0.021</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean insulin (µU/ml)</td>
<td>0.69</td>
<td>0.17</td>
<td>0.007</td>
</tr>
<tr>
<td>Taking diuretic medication</td>
<td>0.33</td>
<td>0.068</td>
<td>0.31</td>
</tr>
<tr>
<td>Taking any antihypertensive medication</td>
<td>-0.10</td>
<td>-0.025</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.0001, for significance of difference from zero.
† BMI, body mass index.
‡ Values at the examination when the first insulin value was recorded.

**TABLE 3.** Multiple linear regression of ΔInsulin on ΔWeight2, Normative Aging Study, 1987–1991

<table>
<thead>
<tr>
<th>Regression term</th>
<th>Coefficient</th>
<th>Standardized coefficient</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.01</td>
<td>-</td>
<td>0.20</td>
</tr>
<tr>
<td>ΔWeight2 (g/year)</td>
<td>-0.03</td>
<td>-0.14</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.01</td>
<td>0.14</td>
<td>0.011</td>
</tr>
<tr>
<td>Taking diuretic medication</td>
<td>-0.035</td>
<td>-0.011</td>
<td>0.87</td>
</tr>
<tr>
<td>Taking any antihypertensive medication</td>
<td>0.01</td>
<td>0.005</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.0001, for significance of difference from zero.
† BMI, body mass index.
‡ Coefficient is the mean difference in insulin change for users compared with nonusers.

**TABLE 4.** Multiple linear regression of ΔInsulin on ΔWeight1, with adjustment for ΔWeight2, body mass index, waist-to-hip ratio, mean insulin, use of diuretic medication, and use of any antihypertensive medication, for all ages combined and stratified by age tertile, Normative Aging Study, 1987–1991

<table>
<thead>
<tr>
<th>Age stratum</th>
<th>Mean age (years)</th>
<th>Range</th>
<th>Regression coefficient on ΔWeight1</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages combined</td>
<td>62.1</td>
<td>44.6-83.0</td>
<td>-0.14</td>
<td>0.15</td>
</tr>
<tr>
<td>Low tertile*</td>
<td>53.8</td>
<td>44.6-58.9</td>
<td>-0.44</td>
<td>0.018</td>
</tr>
<tr>
<td>Medium tertile*</td>
<td>62.0</td>
<td>58.6-65.2</td>
<td>-0.06</td>
<td>0.72</td>
</tr>
<tr>
<td>High tertile*</td>
<td>70.6</td>
<td>65.2-83.0</td>
<td>0.21</td>
<td>0.19</td>
</tr>
</tbody>
</table>

* Significantly different by analysis of variance, p = 0.012.
† H₀, regression coefficient = 0.
drift over the course of the study. Taking change in fasting insulin level as an indicator of change in insulin resistance is likely to be associated with substantial measurement error. Measurement error associated with the insulin assay and additional measurement error associated with fasting insulin as a measure of insulin resistance are likely to have been substantial. We are not aware of any evidence of systematic measurement error with regard to either of these issues. If these errors were randomly distributed, the direction of bias would most likely be toward the null hypothesis, so it is possible that the findings on change in insulin levels and change in obesity may underestimate the true relation between changes in insulin resistance and obesity.

**Obesity and insulin levels**

The physiologic relation between insulin and obesity is far from being completely understood. There are a number of mechanisms (7) that may lead to decreased peripheral sensitivity to insulin mediated glucose uptake in the obese, including increased adipocyte size, decreased numbers of insulin receptors, and increased levels of circulating free fatty acids. On the other hand, there is at least a theoretical mechanism (8) that has some human experimental support (18), by which decreased insulin sensitivity could lead to changes in diet (carbohydrate craving). If the carbohydrate craving lead to increased total caloric intake with no change in energy expenditure, then obesity might arise as a consequence.

Although a wide range of cross-sectional studies have been reported (1), relatively little longitudinal data on insulin and obesity have been published. In a 12-year follow-up of survivors (n = 83) from an original cohort of 107 men in Edinburgh, Scotland, no significant longitudinal changes in fasting insulin levels (19) were observed. Change in weight was significantly correlated with AInsulin. For the association between AWeightl and AInsulin was negative among the youngest men in the Normative Aging Study cohort.

The negative association shown in table 4 might be interpreted as a negative feedback pathway that could act to prevent a vicious cycle of insulin increase and subsequent weight increase implied by the findings discussed below. Evidence of this negative feedback was only observed in the youngest subjects, and this is consistent with the well-known age-related increase in risk of NIDDM.

**Insulin increase predicts weight increase**

The finding of positive weight gain in the following period among individuals whose insulin levels have risen the most (table 5) suggests that among subjects whose insulin levels have recently risen there is a tendency to become more obese.

An analogous finding has been reported from controlled clinical trials (9) of exogenous insulin treatment in NIDDM patients and in uncontrolled clinical trials of insulin-dependent diabetic Native Americans (10). In diabetic patients treated with exogenous insulin, weight gain might be related to more efficient peripheral use of glucose, leaving excess caloric intake available for storage in fat depots. Because clinically diabetic patients were excluded from this study, the mechanism for weight gain following a period of increasing insulin levels is not clear. It is consistent with the suggestion that decreased peripheral insulin sensitivity may disrupt the action of serotonin in me-
dial hypothalamic appetite regulation centers, leading to carbohydrate craving and weight gain (8).

Conclusion

Judgements about causality in complex systems are never simple. One logical prerequisite for a causal relation is that the effect must be seen to take place after the putative cause in terms of temporal sequence. The findings presented here suggest that the dynamics of the relation between insulin levels and obesity are far from straightforward, because changes in either one may precede changes in the other. Physiologic counter-regulatory mechanisms must also be operating, because otherwise there would be a vicious cycle of increasing insulin levels and increasing obesity.

The complex relations among sympathetic nervous activity, insulin, and essential hypertension have been described (20) as a “chicken and egg” situation. Similarly, it seems that the pathophysiologic relation between obesity and insulin is more complex than the conventional epidemiologic notions of cause and effect can readily compass from observational data.

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REFERENCES