Handgrip Strength and Insulin Levels: Cross-sectional and Prospective Associations in the Normative Aging Study

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Hyperinsulinemia is associated with insulin resistance and with the development of diabetes, hypertension, and coronary heart disease. Physical activity appears to be negatively associated with insulin resistance, although the mechanism is unclear. The relationship between physical activity and insulin resistance could be mediated, in part, by direct effects on skeletal muscle, a significant site for insulin-mediated glucose disposal. This report examines the relationship between skeletal muscle strength (as measured by handgrip dynamometry) and fasting insulin levels in a cohort of men in the ongoing Normative Aging Study (NAS). Handgrip strength was negatively associated ($P = .013$) with logarithmic (log) fasting insulin in cross-sectional data from 655 subjects after adjustment for potential confounders including age, body mass index (BMI), ratio of abdominal girth to hip breadth (AG/HB), usual physical activity level, and alcohol intake in a multiple regression model. In data collected prospectively among 1,195 subjects, handgrip strength measured at study entry was negatively predictive of log fasting insulin ($P = .017$) measured 22.9 ± 2.6 years later, after adjustment for age, BMI, and AG/HB at study entry in a multiple linear regression model. A cross-sectional association was confirmed in an analysis of prospective data on the relationship between handgrip strength and fasting insulin levels. The findings suggest that skeletal muscle weakness may precede and predict the development of insulin resistance, and raise the intriguing possibility of some common cause in skeletal muscle pathophysiology.

HIGHER LEVELS OF INSULIN may be detected during the early stages of development of resistance to the glucose-regulatory actions of insulin,[1] and hyperinsulinemia is highly correlated with specialized laboratory-based measures of insulin resistance.[2] Insulin resistance is of importance because it is associated with the development of essential hypertension and non–insulin-dependent diabetes mellitus (NIDDM).[3]

Physical activity appears to be a potentially modifiable life-style factor associated with insulin resistance,[4] hyperinsulinemia,[5] and the risk of NIDDM.[6] Skeletal muscle is one of the major sites for glucose disposal during carbohydrate loading, so it is conceivable that some of the effects of physical activity on insulin resistance are mediated through a direct effect on skeletal muscle physiology.

Increased skeletal muscle strength and endurance may arise through the training effects of physical activity, whereas significant muscular weakness is likely to limit the amount of physical activity that can be undertaken. Although there are a variety of specialized laboratory-based methods of measuring energy expenditure and thus estimating physical activity levels, these are not suitable for epidemiological studies, which generally rely on less precise, questionnaire-based estimates of usual activity. Assessment of skeletal muscle strength by dynamometry is a relatively simple and inexpensive procedure, but there are few published data on the relationship between dynamometry and insulin levels.

The purpose of this study was to examine the cross-sectional and prospective relationships between handgrip dynamometry and fasting insulin levels in the Normative Aging Study (NAS) cohort, with adjustment for potential confounders. Our hypothesis was that lower levels of skeletal muscle strength (as reflected by dynamometry) may be associated with higher insulin levels in cross-sectional data, and may be predictive of the development of higher levels in prospective data.

SUBJECTS AND METHODS

Subjects and Measurements

The NAS is an ongoing longitudinal study established by the Veterans Administration in 1961. Details of the study protocol have been described in detail.[7] Briefly, the original study cohort consisted of 2,280 community-dwelling men from the Boston area who were aged 21 to 80 years at entry, selected from volunteers who were screened according to specific clinical, laboratory, spirometric, radiologic, electrocardiographic, and medical-history criteria[7] so that the subjects were free of known chronic medical conditions at entry.

Each participant reports for a periodic examination including a uniform medical history and physical examination and laboratory blood tests. Subjects fast overnight before the examination. At each visit, fasting blood samples are drawn for laboratory analyses. For a limited period (February 1987 until July 1991), insulin levels from fasting samples were measured using a solid-phase ^{125}I radioimmunoassay (Coat-A-Count; Diagnostic Products, Los Angeles, CA). Interassay and intraassay coefficients of variation were 5% to 7% and 3% to 5%, respectively.

An estimate of usual daily alcohol intake (grams per day) over the past year is obtained from a semiquantitative food-frequency questionnaire (SFFQ)[8,9] that is mailed to all participants and completed before the visit. A questionnaire on usual activity based on the scale of Paffenbarger et al[10] accompanies the SFFQ. Weekly energy expenditure (Kilocalories per week) due to physical activity is estimated from the frequency and duration of various activities, including participation in sports (eg, golf or bowling are assigned 5 kcal/min, aerobics 7.5 kcal/min, and swimming 10 kcal/min) or the number of flights of stairs

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climbed (one flight is assigned 4 kcal) and walking distance (one city block is assigned 8 kcal) each day.

Anthropometry is performed at each visit in accordance with the study protocol. Measurements are taken with the subject standing erect with feet together, clothed in undershorts and socks only. Weight in pounds is measured on a beam balance and converted to kilograms. Stature is measured against a wall chart. Body mass index (BMI) is calculated as weight in kilograms divided by the square of height in meters.[11] The girth of the abdomen is measured in a plane perpendicular to the long body axis at the level of the umbilicus without compression of the skin. The breadth of the hips is measured in the sitting position, with the anthropometer (G.P.M., Gneupel, Switzerland) at the level of the greater trochanters without compression of the soft tissues. The ratio of abdominal girth to hip breadth (AG/HB) is calculated as a measure of the distribution of adiposity; higher values reflect a more central pattern of fat distribution. Handgrip strength is measured with a dynamometer in each hand separately. The mean of the measurements from both hands is used as a measure of skeletal muscle strength.

Analysis

Complete data for each of the analyses were available from only a subset of subjects because of changes in the study protocol and cohort attrition over time. Physical activity, fasting insulin level, and quantitative alcohol intake measurements were added to the study protocol in February 1987 and handgrip dynamometry ceased in March 1989, for an interval of just over 2 years during which all of the variables needed for the cross-sectional analysis were being collected. The total number of subjects with complete data collected during this limited period is 655.

Handgrip dynamometry, BMI, and AG/HB were available from almost all subjects at study entry. Insulin levels were the outcome of interest in the prospective analysis, and these were available from 1,223 subjects, of whom 28 had at least one baseline value missing, leaving 1,195 subjects with complete baseline data for the analysis. The smaller sample size for the cross-sectional analysis as compared with the prospective analysis arose because no measurements of handgrip dynamometry were made at the examination at which fasting insulin level was measured for 568 subjects who were examined during the interval from March 1989 to July 1991. Insulin measurements ceased after July 1991.

Pearson correlation coefficients were estimated from the cross-sectional data. Multiple linear regression was used to model the cross-sectional relationship between handgrip dynamometry and fasting insulin level after adjustment for potential confounders including age, relative adiposity, body fat distribution, alcohol intake, and physical activity.

The prospective relationship between handgrip dynamometry measured at study entry and fasting insulin at follow-up study, with adjustment for potential confounders measured at baseline including age, relative adiposity, and body fat distribution, was examined in a multiple linear regression model. Baseline measures of physical activity, fasting insulin, and alcohol intake were not available for inclusion in these models.

Fasting insulin values were logarithmically (log)-transformed for correlation and regression analyses, because this substantially decreased the skewed distribution of untransformed values. The Statistical Analysis System[12] was used for all analyses.

RESULTS

Cross-sectional Analysis

Characteristics are shown in Table 1 for 655 subjects who had complete data for the cross-sectional analysis. Table 2 shows the correlations between these variables. Handgrip dynamometry was correlated positively with BMI and negatively with both age and a central pattern of fat distribution (AG/HB). Fasting insulin (log-transformed) was correlated positively with BMI and AG/HB and negatively with alcohol intake and physical activity.

Table 1. Cross-sectional Data From NAS Examinations, 1987 to 1989 (N = 655)

Variable	Mean ± SD
Age (yr)	62.1 ± 7.9
Handgrip strength (kg)	45.0 ± 9.6
BMI (kg/m^2)	27.2 ± 3.5
AG/HB	2.62 ± 0.16
Physical activity (MJ/wk)	10.4 ± 9.10
Alcohol (g/d)	15.6 ± 20.0
Fasting insulin (pmol/L)	82.0 ± 59.8

Results of multiple linear regression of fasting insulin on handgrip dynamometry with adjustment for age, BMI, AG/HB, alcohol intake, and physical activity are shown in Table 3. Although handgrip dynamometry was not significantly correlated with the unadjusted fasting insulin level (Table 2), it was a significant negative predictor of fasting insulin after adjustment for potential confounders. Alcohol intake, BMI, and AG/HB were also significant predictors of fasting insulin in this model.

Prospective Analysis

Characteristics for 1,195 subjects who had complete data for the prospective analysis are shown in Table 4. Insulin values were measured at follow-up study between 1987 and 1991, and all other measurements are taken from the first recorded examination for each subject. The 655 subjects in the cross-sectional analyses (Tables 1, 2, and 3) were a subset of these 1,195 subjects. Comparing Table 1 and Table 4, it is clear that at an earlier age, mean handgrip dynamometry was higher and mean BMI and AG/HB were lower compared with the values at follow-up evaluation. The mean fasting insulin in this group was slightly higher than the value in the cross-sectional analysis (Table 1), but this difference was not statistically significant by unpaired t test. There were a total of 27,366 person-years of follow-up study (mean interval, 22.9 ± 2.6 years) between the baseline measurements and the fasting insulin measurements.

Results of multiple linear regression of fasting insulin at follow-up evaluation on baseline characteristics are shown in

Table 2. Correlation Coefficients for Cross-sectional Data From NAS Examinations, 1987 to 1989 (N = 655)

	Age	Handgrip	BMI	AG/HB	Physical Activity	Alcohol	Log Fasting Insulin
Age	1.0	−.41‡	−.16‡	.01	.0003	−.13†	.01
Handgrip		1.0	.12*	−.15‡	.05	.06	−.06
BMI			1.0	.51‡	−.16‡	−.04	.48‡
AG/HB				1.0	−.18‡	.10*	.38‡
Physical activity					1.0	.02	−.10*
Alcohol						1.0	−.10*
Log fasting insulin							1.0

*$P < .01$.
†$P < .001$.
‡$P < .0001$.

Table 3. Results From a Multiple Linear Regression Model for Log Fasting Insulin, With Predictor Variables Measured Contemporaneously From NAS Examinations, 1987 to 1989 (N = 655)

Regression Term	Parameter Estimate ± Standard Error	P	Standardized Estimate
Intercept	−0.70 ± 0.44	.113	
Handgrip dynamometry	−0.0061 ± 0.0024	.013	−0.088
Age	−0.0055 ± 0.0029	.060	−0.073
BMI	0.066 ± 0.0071	.0001	0.371
AG/HB	0.697 ± 0.155	.0001	0.178
Physical activity	0.00013 ± 0.0023	.955	0.002
Alcohol intake	−0.0033 ± 0.0011	.002	−0.107

Table 5. The coefficients are similar to those shown in Table 3 for the cross-sectional data, and indicate that handgrip dynamometry measured at study entry was a significant predictor of fasting insulin levels measured two decades later, after adjustment for potential confounders. Age, BMI, and AG/HB at baseline were also significant predictors of fasting insulin at follow-up study.

DISCUSSION

Major Findings

A negative cross-sectional association between handgrip dynamometry and fasting insulin level was found after adjustment for potential confounders. In data collected prospectively, higher values for baseline handgrip dynamometry predicted lower values for fasting insulin some 20 years later. Although baseline insulin measurements were not available, euglycemia (as indicated by an oral glucose tolerance test) was one of the selection criteria for study entry, so the prospective findings are consistent with a causal relationship because lower skeletal muscle strength preceded fasting hyperinsulinemia. Even if the relationship is not causal, our data suggest that decreased skeletal muscle strength may serve as a marker for the risk of increased insulin resistance as indicated by hyperinsulinemia.[2,13]

Limitations

The measure of skeletal muscle strength used in this study may be falsely low in subjects with substantial arthritis, although this was absent at baseline (since all subjects were screened for chronic disease) and relatively uncommon at the time of insulin measurement in the ongoing NAS cohort. Similarly, although fasting insulin has been recommended as a measure of insulin resistance for epidemiological studies,[2] it is not ideal, being an indirect indicator. However, specialized laboratory-based techniques for measuring insulin resistance

Table 4. Prospective Data from the NAS (N = 1,195)

Variable	Mean ± SD
Age (yr)*	41.5 ± 7.9
Handgrip (kg)*	55.7 ± 8.9
BMI (kg/m²)*	25.8 ± 2.7
AG/HB*	2.54 ± 0.15
Fasting insulin (pmol/L)†	93.0 ± 99.2

*Values taken from study entry examination.
†Measured between February 1987 and July 1991.

Table 5. Results From a Multiple Linear Regression Model for Log Fasting Insulin, With Predictor Variables Measured at Study Entry From the NAS (N = 1,195)

Regression Term	Parameter Estimate ± Standard Error	P	Standardized Estimate
Intercept	2.27 ± 0.35	.0001	
Handgrip Dynamometry	−0.0047 ± 0.0020	.017	−0.071
Age	−0.0084 ± 0.0022	.0001	−0.114
BMI	0.0434 ± 0.0072	.0001	0.201
AG/HB	0.642 ± 0.128	.0001	0.166

are not practicable for large cohorts such as the one reported here. More importantly, in the absence of any evidence of a systematic relationship between measurement error in insulin resistance and in skeletal muscle strength, our results are likely to be an underestimate of the true relationship, since random measurement error would tend to bias the results toward a finding of no association. The cohort consisted entirely of males, and the generalizability of the findings, particularly to females, is not known.

Handgrip Dynamometry and Skeletal Muscle

Handgrip dynamometry is a simple and direct isometric method for assessment of hand and forearm skeletal muscle strength. Maximal isometric strength as recorded on the dynamometer involves a variable mixture of muscle fiber types depending on the time course of the effort, which was not recorded. In adulthood, peak isometric grip strength is attained in the third decade,[14] with a curvilinear decline thereafter.[15] The analyses reported here were adjusted for age to control for confounding, so the effect of increasing age is unlikely to fully explain the findings.

It has been reported that age-related strength losses can be reversed to a large extent by standard physical training program[14] and that dynamometry is positively correlated with physical activity measured using the Paffenbarger instrument.[15] In unadjusted analyses, dynamometry was not significantly correlated with the questionnaire-based measure of physical activity (Table 2), but it was associated positively with BMI and negatively with a central pattern of body fat distribution (AG/HB).

Body composition is often described in terms of adipose tissue (fat mass) and fat-free or lean tissue (eg, muscle and bone) mass.[11] The correlation between BMI and handgrip dynamometry may be a reflection of higher levels of lean body mass, because the numerator in the calculation of BMI, body weight, does not distinguish between lean and fat mass.[11] Conversely, greater AG/HB values are likely to be found in subjects with a greater proportion of fat mass, which may explain the negative association between handgrip dynamometry and AG/HB.

Other Determinants of Hyperinsulinemia

There is recent evidence that alcohol intake is associated with lower levels of insulin resistance.[16,17] This is consistent with the unadjusted correlations between alcohol intake and fasting insulin shown in Table 2 and with the significant negative coefficient on alcohol intake in the multiple linear regression model shown in Table 3.

Both BMI and a central pattern of body fat distribution (as measured by AG/HB) were associated negatively with physical activity. This probably reflects a complex interdependence, since subjects who are less active are likely to store excess dietary energy intake as adipose tissue, while obesity itself may lead to avoidance of physical activity. The positive association between fasting insulin levels and both BMI and AG/HB in the NAS cohort (Table 2) is consistent with many other reports.[18] Our analyses were appropriately adjusted for these potential confounders.

Skeletal Muscle and Hyperinsulinemia

The term "insulin resistance" has a variety of meanings and measurement methods,[1] since insulin is a pleiotropic hormone. Fasting and post–carbohydrate challenge hyperinsulinemia are generally found in subjects in the early stages of the development of insulin resistance,[2,13] although lower levels of insulin may subsequently develop as a consequence of decreased insulin secretory capacity and in association with frank glucose intolerance and diabetes.[3] One consequence of resistance to the glucose-regulatory actions of insulin is decreased tolerance to carbohydrate-loading. In addition to hepatic and adipose tissue, skeletal muscle is a significant site for glucose disposal during carbohydrate-loading,[1] and this activity appears to be facilitated by insulin.

Thus, from a pathophysiological perspective, there is some biological plausibility for a link between lower levels of skeletal muscle strength and development of insulin resistance and hyperinsulinemia. There may be some change in the muscle physiology that is associated with both insulin resistance and muscle weakness. Although no baseline measures of insulin were available, all potential subjects underwent an oral glucose tolerance test at study entry and glucose tolerance was one of the screening criteria for ongoing participation, so these findings suggest that the weakness may substantially predate the hyperinsulinemia.

Increased levels of physical activity were associated with lower levels of fasting insulin in the NAS cohort (Table 2). Physical activity may improve glucose tolerance in diabetics.[19] Higher levels of physical activity may be associated with greater muscle strength as a consequence of training, although this was not evident in the NAS data. On the other hand, weakness may lead to avoidance of physical activity and a vicious cycle of muscle disuse, increased weakness, and increased obesity.

Conclusions

Upper-limb skeletal muscle weakness was associated with a higher level of insulin resistance as measured by the fasting insulin level in cross-sectional analysis. Upper-limb weakness served as a marker for future risk of insulin resistance because it was predictive of higher levels of fasting insulin in prospective data.

Skeletal muscle is one of the major sites of insulin-mediated glucose disposal, and it is biologically plausible that changes in skeletal muscle physiology may result in measurable changes both in muscle strength and in peripheral sensitivity to insulin. Thus, the prospective findings reported here are consistent with the possibility that changes in skeletal muscle strength may serve as a marker for some as yet unknown pathophysiological change in skeletal muscle that is causally linked to the development of weakness, insulin resistance, and subsequent hyperinsulinemia.

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