Factors of the Insulin Resistance Syndrome in Nondiabetic and Diabetic Elderly Japanese-American Men

K. L. Edwards, C. M. Burchfiel, D. S. Sharp, J. D. Curb, B. L. Rodriguez, W. Y. Fujimoto, A. Z. LaCroix, M. V. Vitiello, and M. A. Austin

Factor analysis has previously identified four independent factors that characterize the insulin resistance syndrome in women, interpreted as 1) weight/waist, 2) lipids, 3) insulin/glucose, and 4) systolic and diastolic blood pressure. Because it is not known whether similar factors emerge for men, or for diabetics, factor analysis was used to investigate the clustering of features characterizing the insulin resistance syndrome using data from 3,159 elderly (71–93 years) Japanese-American men participating in the fourth examination of the Honolulu Heart Program during 1991–1993. Consistent with previous results, factor analysis reduced eight risk factors (insulin, glucose, systolic blood pressure, diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol, weight, and waist circumference) to four uncorrelated factors that explained 78.2% and 74.7% of the variance in nondiabetics (n = 2,760) and diabetics (n = 399), respectively. These factors were interpreted as 1) weight/waist, 2) blood pressure, 3) lipids, and 4) insulin/glucose. Modest differences in the associations between fasting insulin and factors 1, 3, and 4 were noted for diabetics. These consistently identified composite factors may represent markers for underlying pathophysiologic mechanisms of the insulin resistance syndrome and risk of non-insulin-dependent diabetes mellitus.

Non-insulin-dependent diabetes mellitus (NIDDM) is an important public health problem among several ethnic groups in the United States, including Mexican- and Native-American populations (1–3). Perhaps less recognized is the increased risk of NIDDM in Japanese-Americans; the prevalence of NIDDM among Japanese-Americans is approximately two to four times greater than among similar-aged white men living in the United States (4, 5). Furthermore, the frequency of NIDDM in Japanese-American men born between 1910 and 1939 is approximately 20 percent, and is similar to Mexican-Americans of the same age (4–6). Thus, NIDDM represents a considerable public health problem among Japanese-Americans.

The insulin resistance syndrome, characterized by a clustering of interrelated risk factors for NIDDM and cardiovascular disease, including dyslipidemia, hypertension, glucose intolerance, obesity, and a predominance of upper body fat (7–9), may also be more prevalent among Japanese-Americans. Although both genetic and environmental factors are involved in NIDDM and the insulin resistance syndrome (10–12), the underlying basis for the clustering of insulin resistance syndrome risk factors remains to be definitively established. By better characterizing the clustering of these risk factors, important insights into the etiology of the insulin resistance syndrome and NIDDM may be gained.

Factor analysis provides a method for investigating such a set of interrelated variables and has been used to examine the clustering of insulin resistance syndrome risk factors in two different samples of Caucasian women, with average ages of 50 and 70 years, respectively (13, 14). Briefly, factor analysis similarly reduced insulin resistance syndrome risk factors, including fasting and postload glucose and insulin, body weight, waist circumference, systolic and diastolic blood pressure, high-density lipoprotein (HDL) cho-
lesterol, triglycerides, and low-density lipoprotein peak particle diameter (a measure of low-density lipoprotein size), to four uncorrelated composite variables, or “factors” (13, 14). In both studies, these factors were interpreted as 1) body mass/fat distribution, 2) insulin/glucose, 3) lipids, and 4) blood pressure (13, 14). The consistency of these findings suggests that the composite factors may represent markers for underlying pathophysiologic mechanisms of the insulin resistance syndrome. However, it is not known if similar factors emerge among men, among diabetics, or among ethnic groups at higher risk for NIDDM.

Thus, the purposes of this paper are 1) to use factor analysis to determine whether the same set of four factors emerge in a sample of older Japanese-American men living in Honolulu, Hawaii, and 2) to then determine if the clustering of features is similar among nondiabetic and diabetic men.

MATERIALS AND METHODS

Study subjects

The Honolulu Heart Program is a longitudinal epidemiologic study initiated in 1965 to identify risk factors for cardiovascular disease among a cohort of 8,006 Japanese-American men living on the island of Oahu and born between 1900 and 1919 (15). The baseline examination, conducted between 1965 and 1968, was followed by two examinations including more than 90 percent of the original cohort. A third comprehensive examination was conducted between 1971 and 1974. Finally, the fourth, and most recent, comprehensive examination of elderly survivors of the cohort was conducted between 1991 and 1993. A total of 4,678 men were eligible for this examination, and 3,742 participated, for a response rate of 80 percent. The data from this examination forms the basis of the present report.

Data collection

Both anthropometric and laboratory measurements were performed as part of the fourth examination. Height and weight were measured with subjects in light clothing and without shoes; body mass index was calculated as weight (kg) divided by height squared (m²). Waist circumference was measured at the level of the umbilicus with the participant standing erect. Blood pressure was measured while the subject was seated using a standard manometer. Systolic blood pressure was defined as the point of first appearance of Korotkoff sounds, and diastolic blood pressure was defined as the point of disappearance of Korotkoff sounds. Two readings were taken on the right arm by a trained technician using an appropriate sized cuff. The average of the two measurements was used in all analyses.

Following a 12-hour overnight fast, samples were collected for lipid and lipoprotein determinations, and were performed using the same laboratory and methods used in the Cardiovascular Health Study (16, 17). Specifically, fasting serum cholesterol, HDL cholesterol, and triglycerides were determined using an Olympus Demand System (Olympus Corporation, Lake Success, NY), and were standardized according to the Centers for Disease Control and Prevention (17).

Plasma glucose and insulin levels were also measured after a 12-hour fast. Insulin determinations were performed at the Diabetes Endocrinology Research Center Core Radioimmunoassay Laboratory, North-west Lipid Research Laboratories, Seattle, Washington, using a double-antibody radioimmunoassay (18). Plasma glucose levels were measured by the glucose oxidase assay (19), at the University of Vermont, Burlington, Vermont.

Information on medication use, including medications for hypertension, cholesterol lowering, and diabetes, was also collected at the time of the examination by a trained interviewer. Diabetes was defined using self-reported history, and/or treatment at the fourth examination.

From the initial sample of 3,742 men, a total of 425 were missing data for either fasting insulin and/or glucose (n = 283), body weight (n = 6), diastolic blood pressure (n = 3), or diabetes status (n = 133), and were excluded from all analyses. An additional 79 men with triglyceride levels greater than 400 mg/dl were excluded from the analysis, and diabetic men who were taking insulin were also excluded (n = 79). After these exclusions, there were 2,760 nondiabetic and 399 diabetic men with complete data included in the analysis.

Statistical analysis

Student’s t test was used to compare mean values of age and other risk factors for the insulin resistance syndrome in nondiabetics and diabetics. Insulin and triglyceride levels were transformed using the natural log, however, the back transformed values are presented in the tables. Relationships between individual features of the insulin resistance syndrome were initially examined using Pearson’s correlation coefficients. Due to the large number of comparisons, a significance level of p < 0.01 was used in all analyses.

Factor analysis. Factor analysis was used to investigate relationships among the correlated risk factors for the insulin resistance syndrome by identifying presumed underlying “factors” stratified by diabetes status (13). Briefly, factor analysis is a three step process:

Am J Epidemiol Vol. 147, No. 5, 1998
1) extraction of the initial components, using principal component analysis, 2) rotation of the components, resulting in factors, and 3) interpretation of the factors (20, 21).

Principal component analysis. Principal component analysis was used to extract the initial set of uncorrelated components (20). For comparison with previous results in women (13, 14), four components were retained in this analysis. However, because post-load insulin and glucose determinations were not available for over 1,100 subjects, postload values were not included in the factor analysis.

Rotation of principal components. Each of the four components was rotated to facilitate their interpretation, and are then referred to as factors. An orthogonal rotation (Varimax rotation) was used in this analysis to obtain the factors, maintaining their independence (20, 22). That is, each factor is statistically uncorrelated with every other factor.

Interpretation of factors. Factor loadings, equivalent to Pearson's correlation coefficients between each variable and each factor, were used to interpret the factors. However, only those variables sharing at least 15 percent of the variance with the factor were used for interpretation (20), corresponding to a factor loading with an absolute value ≥0.40. Although not used for interpretation, significant factor loadings (p < 0.01) are also noted in the tables. SAS software was used for all analyses (23).

RESULTS

Table 1 presents characteristics of the study sample and descriptive statistics. The average age of men in this study was approximately 77 years (range 71 to 93 years), and was nearly identical for nondiabetic and diabetic men. On average, nondiabetics weighed significantly less, had a smaller waist circumference, and higher HDL cholesterol levels. Mean levels of log-transformed triglycerides were not significantly different in nondiabetes compared with diabetics, although the mean value was higher for diabetics. As expected, log-transformed fasting insulin and glucose levels were significantly lower among nondiabetics (p < 0.01), compared with diabetics. Diastolic blood pressure was significantly higher in the nondiabetic subjects, however, there was no statistically significant difference in systolic blood pressure.

Correlations among the variables of the insulin resistance syndrome are reported separately for nondiabetic and diabetic study subjects in table 2. Among both nondiabetic and diabetic subjects, body weight and waist circumference were highly, and significantly, correlated. Also, in both nondiabetics and diabetics, HDL cholesterol was significantly inversely correlated with body weight and waist circumference, while triglycerides showed positive correlations with these variables. As expected, triglycerides and HDL cholesterol were significantly inversely correlated (13) in both groups. Fasting glucose was inversely correlated with HDL cholesterol in both nondiabetic and diabetic subjects, but was not significant. Systolic and diastolic blood pressure were significantly correlated with each other, but were not strongly associated with any other risk factor, in both groups.

Although most correlations were similar in nondiabetics and diabetics, some differences were noted. Fasting insulin was inversely correlated with HDL cholesterol in nondiabetics, however, the correlation was not significant among diabetics. Similarly, the correlations between fasting insulin and both HDL cholesterol and triglycerides were reduced to nonsignificant levels in the diabetic subjects. Finally, the correlations between fasting insulin and body weight, waist circumference, and fasting glucose were reduced but remained significant in the subjects with diabetes.


<table>
<thead>
<tr>
<th></th>
<th>Nondiabetics (n = 2,760)</th>
<th>Diabetics (n = 399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77.6 (4.6)</td>
<td>77.4 (4.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.1 (9.4)</td>
<td>62.8* (10.3)</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>85.8 (8.6)</td>
<td>87.4* (9.3)</td>
</tr>
<tr>
<td>HDL† cholesterol (mg/dl)</td>
<td>52.0 (13.1)</td>
<td>48.8* (13.7)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>124.2 (1.6)</td>
<td>131.4 (1.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>149.5 (23.3)</td>
<td>151.1 (23.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.4 (11.0)</td>
<td>77.7* (11.6)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>105.8 (15.7)</td>
<td>149.1* (44.8)</td>
</tr>
<tr>
<td>Fasting insulin (mg/dl)</td>
<td>12.0 (1.7)</td>
<td>15.3* (1.6)</td>
</tr>
</tbody>
</table>

* p < 0.01, based on Student's t test.
† HDL, high density lipoprotein; SD, standard deviation.
Factor analysis

As shown in tables 3 and 4, four components were retained in the factor analysis, explaining 78.2 percent and 74.7 percent of the variance in the data for nondiabetics and diabetics, respectively.

Among nondiabetics (table 3) factor 1 was characterized by positive factor loadings for body weight, waist circumference, diastolic blood pressure, triglycerides, fasting insulin, and fasting glucose. Systolic blood pressure and HDL cholesterol were negatively correlated with this factor. Of these variables, only body weight, waist circumference, and fasting insulin were significantly correlated with factor 1. Due to the large factor loadings for body weight and waist circumference, this factor was interpreted as a "body weight/fat distribution" factor, and explained 25.0 percent of the variance in the data.

Among diabetics (table 4), factor 1 was characterized by positive factor loadings for body weight, waist circumference, diastolic blood pressure, triglycerides, fasting insulin, and fasting glucose. Systolic blood pressure and HDL cholesterol were negatively correlated with this factor. Of these variables, only body weight, waist circumference, and fasting insulin were significantly correlated with factor 1. Due to the large factor loadings for body weight and waist circumference, this factor was interpreted as a "body weight/fat distribution" factor, and explained 25.0 percent of the variance in the data.
Factors of the Insulin Resistance Syndrome in Japanese-American Men

In this study, factor analysis was used to reduce interrelated risk factors for the insulin resistance syndrome to four uncorrelated factors in a sample of more than 3,000 older, Japanese-American men. Four factors that together explained over 75 percent of the variance in the data, were identified in both non-diabetic and diabetic subjects and were interpreted as: 1) body weight/fat distribution, 2) blood pressure, 3) lipids, and 4) insulin/glucose.

These four factors identified in men are very similar to those identified in two previous reports of nondiabetic women (13, 14). First, in a sample of younger women (mean age 49.7 ± 12.6 years), four factors were identified and interpreted as: 1) body weight/fat distribution, 2) insulin/glucose, 3) lipids, and 4) blood pressure. In addition to comparable interpretations for each of the four factors, the factor loadings themselves were also very similar in magnitude to those reported here. For example, the factor loadings for the body weight/fat distribution factor were 0.92, 0.87, and 0.61 for body weight, waist circumference, and fasting insulin, respectively (13), compared with 0.93, 0.92, and 0.46, respectively, in this study (table 3), and 0.91, 0.83, and 0.46, respectively, in older women (14). It is interesting to note that the body weight/fat distribution factor explained the largest proportion of total variance in the data in each of the three studies (ranging from 20 to 25 percent). Finally, the consistent identification of a “body weight/fat distribution” factor across these three different groups may reflect a common role for this combination of risk factors in the insulin resistance syndrome, and possibly NIDDM.

Also consistent with previous results is the identification of a blood pressure factor. This factor has had remarkably similar factor loadings for systolic and diastolic blood pressure across all three groups; 0.88 for both systolic and diastolic blood pressure in this study, compared with 0.84 and 0.85, respectively, in postmenopausal women (14), and 0.86 for both in younger women (13). Interestingly, the blood pressure factor explained a slightly larger proportion of the total variance in both older men and older women (approximately 14 percent), compared with 9 percent in the sample of younger women (13, 14). Further, blood pressure was not highly correlated with lipid values in this study, or in the two previous studies in women (13, 14).

Postload glucose and insulin were not included in this analysis of Japanese-American men since only a subset of the men received an oral glucose tolerance test (n = 2,023), and because postload insulin is a less reliable marker of insulin resistance among diabetics (24). Despite this difference, a similar insulin/glucose factor emerged, although the proportion of variance explained by this factor was slightly less than in the two previous reports in women, 14 percent versus approximately 16–22 percent, respectively (13, 14). Although a measure of low density lipoprotein size heterogeneity was also not available in this sample, a similar lipid factor also emerged for men, and consis-
tently explained approximately 20 percent of the total variance in men (13, 14).

Overall, very similar factors explaining over 74 percent of the variance were identified in older Japanese-American men, postmenopausal women (14), and a sample of younger women (13). The consistency of these findings in three different samples, including an ethnic group at increased risk for NIDDM, and spanning a wide range of ages, supports the hypothesis that the clustering of risk factors identified by factor analysis may represent meaningful, underlying physiologic associations.

Further, this large sample of Japanese-Americans, including nearly 400 diabetic men who were not taking insulin, provides a unique opportunity to compare the clustering of these risk factors among nondiabetics and diabetics. Although factor 2 was virtually identical among diabetics and nondiabetics, and factors 3 and 4 were similar, interesting differences were noted for factor 1, the body weight/fat distribution factor. The increased factor loading for fasting insulin on the body weight/fat distribution factor among nondiabetics (0.46 (table 3), compared with diabetics (0.16 (table 4)), suggests that the interrelations between body weight, fat distribution, and fasting insulin are stronger among nondiabetics. This finding may reflect the importance of adiposity in insulin resistance, and is consistent with previous studies (25–30). For example, studies of Japanese-Americans living in Seattle, Washington, have shown that individuals with visceral adiposity are more insulin resistant than those who have less visceral adiposity (25, 26).

An important limitation of this study is the use of self-reported diabetes. It is well known that approximately half of the individuals with diabetes are unaware of their condition (1, 31). This form of misclassification would tend to diminish differences between nondiabetics and diabetics. Thus, it is possible that the patterns observed here do not fully characterize differences in the clustering of insulin resistance syndrome risk factors between nondiabetic and diabetic subjects.

Also, given the advanced age of this cohort, selection bias, including selective survival, must be considered in the interpretation of these results. In particular, it is likely that individuals participating in the fourth examination were healthier than those not participating (32, 33), and thus may not be representative of the original sample. In fact, baseline data from the first examination was compared for individuals participating in the fourth examination with those not participating (living nonparticipants and participants deceased since baseline, n = 4,161). These two groups were found to be significantly different (p < 0.05) with regard to blood pressure (nonparticipants had higher values), blood glucose (nonparticipants had higher values), and body weight (nonparticipants had lower values). Finally, baseline data for participants in the fourth examination was compared with the living nonparticipants (n = 795 nonparticipants). Blood glucose and systolic blood pressure were found to be significantly different between the two groups (p < 0.001), with nonparticipants having higher values. These results are consistent with selection bias. Thus, it is possible that the patterns observed here do not fully characterize the clustering of insulin resistance syndrome risk factors, or the differences between nondiabetic and diabetic subjects. However, it is likely that these results underestimate the true multivariate associations.

Finally, because four very similar factors have now been identified in two different ethnic groups, men and women, and across a wide range of ages, and because a previous analysis has shown that these “factors” are heritable (34), it is tempting to speculate that underlying genetic influences are also involved in the clustering of insulin resistance syndrome risk factors in this sample of Japanese-American men. Other studies have also provided evidence for genetic influences on insulin levels (35, 36), insulin resistance itself (37, 38), and NIDDM (11, 39–41) in several ethnic groups. Thus, it will be important to determine if the clustering of risk factors identified by factor analysis is influenced by the same or different genes in different populations, and whether these “factors” segregate in families with NIDDM. However, it should also be noted that the two- to fourfold increased prevalence of NIDDM in migrant Japanese, compared with nonmigrants, clearly implicates environmental influences in NIDDM as well (42, 43), possibly implying the presence of genetic-environmental interactions.

In conclusion, the results of this study confirm the presence of four underlying factors characterizing the interrelated risk factors of the insulin resistance syndrome in a sample of elderly Japanese-American men, and are consistent with previous results in women. In all three groups, these factors were interpreted as: 1) body weight/fat distribution, 2) blood pressure, 3) lipids, and 4) insulin/glucose. Furthermore, the results of the current study suggest that, although diabetes may influence the level of individual risk factors, it does not appear to alter the underlying associations between most of the risk factors of the syndrome, although the interrelations between body weight, fat distribution, and fasting insulin are altered in diabetics. Identifying the basis for this clustering may provide important insights into the complex etiology of NIDDM.
REFERENCES

19. Keston AS. Specific colorimetric enzymatic analytical reagents for glucose. (Abstract). In: Abstracts of papers for the 129th Meeting of the American Chemical Society, Dallas, Texas, April 8–13, 1956:31C.