The Insulin Resistance Syndrome in Native Hawaiians

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OBJECTIVE — To investigate whether fasting hyperinsulinemia is associated with a clustering of cardiovascular disease (CVD) risk factors, manifesting as the insulin resistance syndrome (IRS), in a population of native Hawaiians.

RESEARCH DESIGN AND METHODS — A total of 574 native Hawaiians ≥30 years of age were examined for blood pressure, waist-to-hip ratio (WHR), BMI, oral glucose tolerance, and fasting lipid, insulin, and C-peptide concentrations. All statistical analyses ($n = 384$) excluded 190 individuals who had NIDDM or who were taking hypertension medication. Using logistic regression analysis, fasting insulin and C-peptide levels were compared with CVD risk factors (glucose intolerance, hypertension, central adiposity, elevated triglyceride levels, and low HDL cholesterol levels) after adjusting for age and obesity.

RESULTS — Sixty-six percent of native Hawaiians were overweight or obese, and 70% were found to have central adiposity. Fasting insulin concentrations were correlated with BMI, WHR, blood pressure, and triglyceride, HDL cholesterol, and glucose concentrations. Fasting insulin was also significantly associated with an increasing number of CVD risk factors in each participant ($P < 0.001$). Fasting insulin and C-peptide concentrations were independently associated with glucose intolerance, high triglyceride levels, and low HDL cholesterol levels. However, only fasting C-peptide concentrations were independently associated with hypertension and central adiposity. Apparent differences in the correlates of fasting insulin and C-peptide may be related to multiple factors and warrant further evaluation.

CONCLUSIONS — This study provides cross-sectional data confirming the existence of the IRS in native Hawaiians. However, further longitudinal studies are needed to examine the relationship of insulin resistance and/or surrogate markers to increased rates of NIDDM and CVD mortality in native Hawaiians.

Asian and Pacific Islander Americans are the fastest-growing minority in the U.S. and their numbers are predicted to quadruple by the year 2038 (1). Within this group, native Hawaiians comprise ~60% of the estimated 365,000 Pacific Islanders and represent the single largest ethnic group of Pacific Island origin in the U.S. (1). Native Hawaiians also have increased rates of obesity (2), heart disease (3), and diabetes (4) and the highest cardiovascular mortality rate in Hawaii (5). Reports of disproportionately increased levels of several cardiovascular disease (CVD) risk factors in native Hawaiians suggest the existence of an underlying metabolic abnormality such as hyperinsulinemia and/or insulin resistance.

The insulin resistance syndrome (IRS), defined as the association of hyperinsulinemia with the clustering of glucose intolerance, increased blood pressure, elevated triglyceride levels, and low HDL cholesterol levels, has been studied in many diverse populations (6–9). However, observed differences in manifestations of the IRS among populations with high rates of diabetes and CVD risk factors emphasize the need for caution in generalizing results to similar ethnic groups such as native Hawaiians (6,8,10). For example, prospective studies in Pima Indians found fasting insulin levels predictive of NIDDM but not associated with the incidence of electrocardiographic abnormalities as a marker for heart disease (11). In addition, other features of IRS have been variable in different ethnic populations, even among ethnic groups with similar rates of obesity and diabetes. Hypertension, for example, is not associated with insulin resistance in blacks and Pima Indians as it is in Caucasians (12,13). By contrast, hypertension is associated with fasting insulin levels in Mexican-Americans and non-Hispanic whites but only in lean individuals (9). In addition, the relationship of blood pressure and fasting insulin levels was also variable in three Pacific Island populations (14) and in a multi-ethnic population of over 5,000 adults in Mauritius (15,16).

Little is known about the relationship of hyperinsulinemia and/or IRS to high rates of CVD mortality and diabetes in native Hawaiians. Variable results among other ethnic groups also suggest that existing data may be of limited relevance to the native Hawaiian population. Thus, this study was undertaken to investigate whether hyperinsulinemia in association with a clustering of CVD risk factors, manifesting as IRS, exists in a population of native Hawaiian adults.

RESEARCH DESIGN AND METHODS

— To conduct this study, researchers at the University of Hawaii formed a partnership with existing Native Hawaiian Health Care (NHHC) organizations for the state (Papa Ola Lokahi, the administrative arm) and the communities of North Kohala (Hui Malama Ola Na 'Oiwi) and West Kauai (Ho'ola Lahui Hawaii). This study was approved by the Committee on Human Studies of the University of Hawaii at Manoa and by both NHHC community advisory boards. All participants gave informed consent before the research examination.

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Abbreviations: CVD, cardiovascular disease; IRS, insulin resistance syndrome; LR, likelihood ratio; NHHC, Native Hawaiian Health Care; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

Table 1—*Distribution of physical and biochemical characteristics of rural native Hawaiians: NHHR Project, 1993–1996* (n = 574)

Age (years)	47.6 ± 12.5
BMI (kg/m²)	30.9 ± 7.0
WHR	0.87 ± 0.08
Systolic blood pressure (mmHg)	128.5 ± 18.2
Diastolic blood pressure (mmHg)	82.7 ± 11.8
Total cholesterol (mmol/l)	5.24 ± 1.08
Triglyceride (mmol/l)	1.70 ± 1.58
HDL (mmol/l)	1.06 ± 0.32
Calculated LDL (mmol/l)	3.43 ± 0.96
Fasting glucose (mmol/l)	6.4 ± 2.5
2-h glucose (mmol/l)	7.1 ± 3.1
Fasting insulin (pmol/l)	128.3 ± 99.9
Fasting C-peptide (nmol/l)	0.74 ± 0.41

Data are means ± SD.

Briefly, North Kohala and West Kauai are rural communities located geographically at opposite ends of the island chain. A total of ~1,100 native Hawaiian adults ≥30 years of age were identified via door-to-door census in both communities. The percentage of native Hawaiian ancestry was determined by self-report, using a modified algorithm adapted to the native Hawaiian population (17). All eligible nonpregnant native Hawaiian adults were invited to participate in a 3- to 4-h examination performed by trained community staff members at the on-site research clinic. All participants fasted 10–12 h before the fasting blood sampling, and individuals not taking insulin or oral diabetic medications were given a 75-g 2-h oral glucose tolerance test (OGTT) (18). Waist and hip circumferences were measured in the standing position, and BMI was computed by weight (in kilograms) divided by height (in meters) squared (19). Blood pressure measurements were performed and recorded as the average of the second and third measurements (20).

Biochemical analyses

Plasma glucose levels were assayed in duplicate, using the glucose oxidase method on an autoanalyzer. Fasting insulin and C-peptide concentrations were measured by radioimmunoassay using commercially available kits (Linco Research, St. Louis, MO, for insulin; Diagnositics Products, Los Angeles, CA, for C-peptide). Intra- and inter-assay coefficient of variations were 4.7 and 4.6%, respectively, for insulin and 3.4 and 4.5%, respectively, for C-peptide. Fasting triglyceride and total and HDL cholesterol assays were performed in compliance with the Centers for Disease Control–National Heart, Lung, and Blood Institute Standardization Program at Penn Medical Laboratories in Washington, DC (21). LDL cholesterol was computed using the Friedwald equation if the triglyceride concentration was <4.5 mmol/l (400 mg/dl) (22).

For the purposes of determining the relationship of fasting insulin or C-peptide to CVD risk factors, each variable was categorized as normal or abnormal as defined by the following standard clinical criteria. Glucose intolerance (impaired glucose tolerance or diabetes) was determined by OGTT, using World Health Organization criteria, or by medical history (18). Hypertension was defined by previous history or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (23). Individuals with a previous history of hypertension but not on medication were considered normotensive if their recorded blood pressure was <140/90 mmHg. Abnormal lipid concentrations were defined as total cholesterol >5.2 mmol/l, triglyceride >2.3 mmol/l, HDL cholesterol <0.9 mmol/l, or LDL cholesterol >3.4 mmol/l (18). Individuals were categorized as overweight if BMI was >27.8 kg/m² in men and >27.3 kg/m² in women (24). Severely overweight or obese individuals were defined as BMI >31.1 kg/m² for men and >32.3 kg/m² for women (24). Adverse body fat distribution or central adiposity was determined by WHR measurements >0.90 in men and >0.80 in women (25).

Statistical analyses

Means and standard deviations for continuous variables were estimated using all participants with complete data (n = 574). All statistical analyses (n = 384) excluded 190 participants who had NIDDM or who were taking hypertension medication. Univariate correlations between fasting insulin and C-peptide levels and each continuous variable (BMI, WHR, age, fasting glucose, 2-h glucose, etc.) were estimated using Spearman's rank correlation. Logistic regression was used to estimate crude and adjusted prevalence odds ratios. The natural logarithm of fasting insulin and C-peptide concentrations was used in all logistic analyses to stabilize variances and normalize skewed distributions. Continuous data on CVD risk factors (glucose intolerance, hypertension, dyslipidemia, etc.) were coded dichotomously according to standard clinical criteria described previously. Prevalence odds ratios and 95% CIs were calculated between the midpoints of the lowest and highest tertile for insulin and C-peptide levels, with each CVD risk factor using logistic regression. Where appropriate, insulin resistance markers (fasting insulin and C-peptide levels) were assessed for a multiplicative interaction with continuous variables by including a cross-product term in the logistic regression model. Finally, to examine the relationship between the clustering of CVD risk factors and fasting insulin and C-peptide concentrations, each participant was categorized by the number of risk factors present and then regressed on fasting insulin levels, using an ordinal polytomous logistic model (26). Model fit was tested using the likelihood ratio (LR) test, and prevalence odds ratios were calculated to assess the strength of the association (27). All statistical analyses were performed using JMP statistical software from SAS Institute (Cary, NC) (28).

RESULTS — A total of 574 individuals (50% response), consisting of 60% women and 40% men with a mean age of 48 years, completed the research examination (Table 1). A high proportion (66%) of both men and women were found to be overweight, with more than half of these individuals (39%) severely overweight. As expected, mean waist-to-hip ratio (WHR) measurements were greater in men than in women; however, the proportion of men and women with adverse fat distribution was similar (69% in men vs. 71% in women). Sex differences were also noted for blood pressure and triglyceride and fasting glucose levels (all higher in men) and for HDL cholesterol levels (higher in women) (data not shown). However, no significant sex differences were found for fasting insulin or C-peptide concentrations.

Significant univariate correlations were found between fasting insulin concentrations and BMI, WHR, blood pressure (systolic and diastolic), and triglyceride, HDL cholesterol, and glucose (fasting and 2-h) concentrations (Table 2). Fasting insulin levels were not significantly related to age or total or LDL cholesterol levels. In comparison with insulin, fasting C-peptide showed equivalent or stronger correlations with each continuous variable.

Using logistic regression, the prevalence odds ratios of fasting insulin and C-peptide

Table 2—*Spearman's rank correlations between fasting insulin and C-peptide levels with selected cardiovascular risk factors, excluding participants with diabetes or who were taking hypertension medications: NHHR Project, 1993–1996* (n = 384)

	Fasting insulin		Fasting C-peptide	
Variable	Spearman's ρ	*P* value	Spearman's ρ	*P* value
Fasting C-peptide	0.627	<0.001	1.000	—
Fasting insulin	1.000	—	0.627	<0.001
Age	−0.086	NS	−0.022	NS
BMI	0.598	<0.001	0.547	<0.001
WHR	0.221	<0.001	0.207	<0.001
Systolic blood pressure	0.153	0.003	0.246	<0.001
Diastolic blood pressure	0.223	<0.001	0.313	<0.001
Total cholesterol	0.036	NS	0.109	0.03
HDL cholesterol	−0.378	<0.001	−0.348	<0.001
LDL cholesterol	−0.018	NS	0.055	NS
Triglycerides	0.402	<0.001	0.396	<0.001
Fasting glucose	0.314	<0.001	0.373	<0.001
2-h glucose	0.379	<0.001	0.336	<0.001

uniformly showed moderate-to-strong associations with each CVD risk factor (Tables 3 and 4, model 1). General obesity was the CVD risk factor found to have the strongest association with fasting insulin and C-peptide concentrations (prevalence odds ratios of 5.67 for insulin and 11.81 for C-peptide). However, after adjusting for general obesity, fasting insulin and C-peptide levels were significantly associated only with glucose intolerance and low HDL cholesterol and high triglyceride levels (Tables 3 and 4, model 2). C-peptide was also significantly associated with central adiposity and hypertension (Table 4, model 2).

Since fasting insulin was not associated with central adiposity after adjusting for BMI, logistic regression was used to test for an interaction among these factors. A significant interaction was found and suggests that the relationship of central adiposity with fasting insulin ($\chi^2 = 13.81$, $P < 0.001$) and fasting C-peptide ($\chi^2 = 12.88$, $P < 0.001$) differs among obese and nonobese individuals. After adjusting for BMI, fasting insulin was significantly associated with central adiposity only in nonobese (BMI <27.8 kg/m^2 in men and <27.3 kg/m^2 in women) individuals.

As illustrated in Fig. 1, an increasing number or aggregation of CVD risk factors in an individual was associated with an increased likelihood of higher fasting insulin and C-peptide levels. This relationship was highly significant, even after adjusting for BMI (unadjusted LR = 28.9, $P < 0.001$ vs. BMI-adjusted LR = 13.7, $P < 0.001$). Thus, individuals in the highest tertile of fasting insulin were, on average, twice as likely to have more CVD risk factors than those in the lowest tertile of fasting insulin (BMI-adjusted prevalence odds ratios 2.07, 95% CI 1.44–2.99). In comparing C-peptide with a cluster of CVD risk factors, the association was of equal significance to fasting insulin concentrations.

CONCLUSIONS — This study provides data to support the association of fasting hyperinsulinemia with glucose, blood pressure, WHR, BMI, and glucose, triglyceride, and HDL cholesterol levels in a population of native Hawaiian adults. In addition, the incremental clustering of CVD risk factors (i.e., glucose intolerance, hypertension, dyslipidemia, central adiposity) was associated with plasma markers of insulin resistance (fasting insulin and C-peptide concentrations) and supports the existence of the IRS among native Hawaiians.

Interestingly, fasting insulin (versus fasting C-peptide) concentrations were not independently associated with central adiposity and hypertension after adjusting for obesity. However, a similar divergence of fasting insulin and C-peptide with visceral adiposity has been found in Japanese-Americans (29). These authors found that only fasting C-peptide levels were associated with intra-abdominal fat and NIDDM incidence and speculated that this difference may be related to clearance rates of C-peptide versus insulin. Among native Hawaiians, only fasting C-peptide levels were significantly associated with central adiposity and parallels the relationship found between C-peptide and intra-abdominal fat reported in Japanese-Americans. The clearance rates of C-peptide levels were not evaluated in this study. However, future studies are needed to examine the clinical significance of C-peptide versus fasting insulin levels as surrogate markers for insulin resistance in native Hawaiians and perhaps other minority populations.

Another possible explanation for the lack of significance between central adiposity and fasting insulin levels may be related to the high prevalence of obesity among native Hawaiians in this study. A similar finding was noted in Nauruans, a population known to have high rates of obesity, in which WHR was not associated with fasting insulin levels in men (30). In Mexican-Americans, another population with increased rates of obesity, a similar

Table 3—*Prevalence odds ratio for selected cardiovascular risk factors, estimated by logistic regression with the logarithm of fasting insulin treated as a continuous variable, excluding participants with diabetes or who are taking hypertension medications: NHHR Project, 1993–1996* (n = 384)

Variable	Model 1*	Model 2†
General obesity	5.67 (3.41–9.43)	—
Central adiposity	2.02 (1.35–3.02)	1.22 (0.74–2.03)
Glucose intolerance‡	2.06 (1.41–3.02)	1.55 (1.00–2.39)
Systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg	1.56 (1.09–2.23)	1.44 (0.95–2.19)
HDL cholesterol <0.9 mmol/l	1.83 (1.28–2.62)	1.51 (1.00–2.29)
Triglycerides >2.3 mmol/l	2.49 (1.41–4.42)	2.82 (1.71–4.65)

Data are odds ratios (95% CIs). Odds ratios were estimated at 171.3 vs.78.6 pmol/l, the means for the last and first insulin tertiles, respectively. *Unadjusted; †adjusted for BMI and age; ‡impaired glucose tolerance,WHO criteria.

Table 4—*Prevalence odds ratio for selected CVD risk factors estimated by logistic regression with the logarithm of fasting C-peptide treated as a continuous variable, excluding participants with diabetes or who are taking hypertension medications: NHHR Project, 1993–1996* (n = 384)

Variable	Model 1†	Model 2‡
General obesity	11.81 (5.20–11.81)	—
Central adiposity	4.26 (2.29–4.26)	2.39 (1.28–3.66)
Glucose intolerance‡	4.93 (2.32–4.93)	3.88 (1.68–6.62)
Systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg	3.86 (1.97–3.86)	2.52 (1.20–4.29)
HDL cholesterol <0.9 mmol/l	3.70 (2.01–3.70)	2.87 (1.48–4.40)
Triglycerides >2.3 mmol/l	6.30 (2.71–6.30)	6.25 (2.39–10.87)

Data are odds ratios (95% CIs). Odds ratios were estimated at 1.08 vs. 0.05, the means for the last and first C-peptide tertiles, respectively. *Unadjusted; †adjusted for BMI and age; ‡impaired glucose tolerance, WHO criteria.

"ceiling" or "plateauing" effect of centrality on glucose sum during an OGTT and on NIDDM prevalence was also noted in men (31). This hypothesis is further supported among native Hawaiians by the significant interaction found between BMI and fasting insulin, resulting in a significant association of central adiposity and fasting insulin levels only in nonobese native Hawaiians. Unfortunately, reports on Nauruans and Mexican-Americans have not included fasting C-peptide levels, thus making comparisons of data in native Hawaiians with populations with similar rates of obesity difficult. Thus, although central adiposity has been linked to markers of insulin resistance in other populations, native Hawaiians appear to differ from most studies in that central adiposity was not independently associated with fasting insulin levels.

Hypertension has been documented to be insignificantly or variably associated with measures of insulin resistance in at least four different ethnic populations, and this finding is also present in native Hawaiians (12–15). Among native Hawaiians, a weak association of hypertension with fasting insulin levels suggests that other factors may play a stronger role in the etiology and clinical manifestation of hypertension. A similar relationship has been described in African-Americans in which salt-sensitivity and vascular hyperadrenergic responsiveness may have a closer link to hypertension than insulin resistance (32). In native Hawaiians, the independent association of fasting C-peptide levels with hypertension contrasts with the lack of association found with fasting insulin. This study did not examine the relationship between insulin sensitivity and fasting insulin or C-peptide levels; thus, we can only speculate that differences between fasting insulin and C-peptide concentrations may represent quantitative differences, since both markers share qualitative similarities with the clustering of CVD risk factors, defined as IRS. Evidence supporting this was recently reported in Japanese-Americans in whom both fasting insulin and C-peptide levels were significantly associated with intra-abdominal fat accumulation. However, the strength of that association was greater with fasting C-peptide than fasting insulin levels (33).

In summary, we found a syndrome of insulin resistance in native Hawaiians characterized by fasting hyperinsulinemia in association with the clustering of CVD risk factors such as glucose intolerance, central adiposity, hypertension, and elevated triglyceride and lowered HDL cholesterol levels. However, central adiposity and hypertension were not independently associated with fasting insulin levels after adjusting for obesity, and this may be related to the high prevalence of obesity and/or other yet-unidentified factors in native Hawaiians. Fasting C-peptide concentrations parallel many of the associations found with fasting insulin. The significance of fasting C-peptide levels, compared with fasting insulin, is unknown and warrants future evaluation among native Hawaiians and other ethnic populations.

One of the limitations of this study is the cross-sectional nature of the data, which maybe subject to the biases inherent in such studies. Thus, further longitudinal studies are needed to evaluate the underlying pathogenesis of hyperinsulinemia, insulin resistance, and the development of CVD risk factors in native Hawaiians. This study was limited to examining common CVD risk factors associated with IRS; however, future studies in native Hawaiians should also consider the role of other emerging risk factors, such as small dense LDL cholesterol and plasminogen activator inhibitor-1, which will provide further insight into the relationship of insulin resistance, ather-

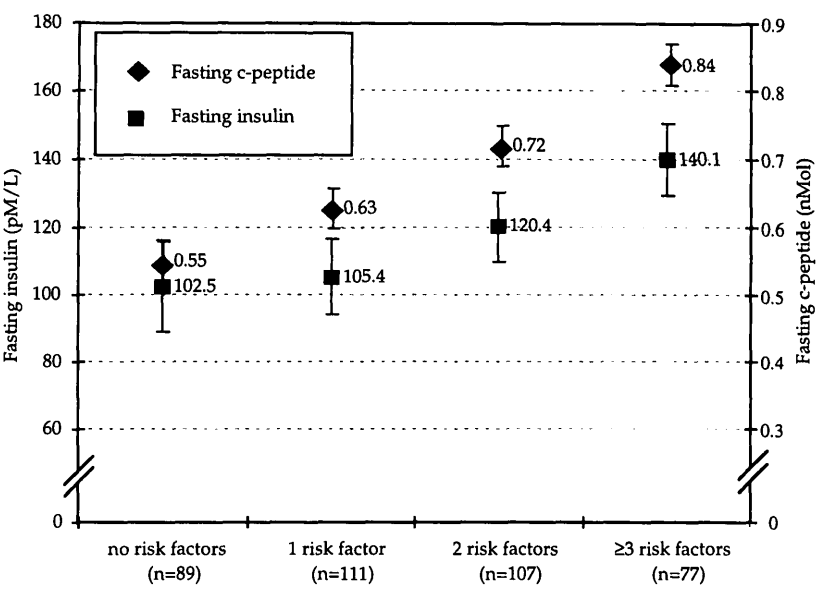

Figure 1—*Least square means of fasting insulin by cumulative number of cardiovascular risk factors present (impaired glucose tolerance, abnormal lipid concentrations [triglycerides >2.3 mmol/l or HDL cholesterol <0.9 mmol/l], hypertension [by history or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg], or central adiposity [WHR >0.90 in men and >0.80 in women]), after adjusting for BMI* (n = 384), *excluding participants with diabetes or those who are taking hypertension medication: NHHR Project, 1993–1996* (n = 384).

osclerosis, and excessive rates of heart disease mortality among native Hawaiians.

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APPENDIX: THE NHHR PROJECT STAFF

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