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Metabolic and adipose risk factors for NIDDM and coronary disease in third-generation Japanese-American men and women with impaired glucose tolerance

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Summary Since second-generation (Nisei) Japanese Americans are prone to develop the insulin resistance syndrome, younger third-generation (Sansei) Japanese Americans from a cross-sectional 10% volunteer sample of Sansei men ($n = 115$) and women ($n = 115$) 34 years or older in King County, Washington with normal glucose tolerance or IGT were examined for metabolic and adipose risk factors associated with this syndrome. After an overnight 10-h fast, blood samples were taken for measurement of glucose, insulin, C-peptide, lipids, and lipoproteins, followed by a 3-h 75-g oral glucose tolerance test with blood samples taken for glucose, insulin, and C-peptide measurement. BMI (kg/m^2), skinfolds, and body fat areas (by computed tomography) were measured. IGT was diagnosed in 19% of the men and 31% of the women. Men with IGT had more adiposity, both overall and in thoracic and visceral sites, had higher fasting plasma insulin and C-peptide, and tended to have higher fasting triglyceride and lower HDL cholesterol than men with normal glucose tolerance. Women with IGT had more thoracic subcutaneous fat and intra-abdominal fat and lower fasting HDL cholesterol than women with normal glucose tolerance, and tended to have higher fasting triglyceride and LDL cholesterol. Women with IGT also had higher fasting plasma insulin than women with normal glucose tolerance but tended to be less hyperinsulinaemic than men. Differences in fasting insulin, C-peptide, and lipids were best predicted by intra-abdominal fat. Thus metabolic (higher fasting insulin and a tendency to higher triglyceride and lower HDL cholesterol) and adipose (visceral adiposity) risk factors associated with the insulin resistance syndrome are identifiable among Sansei men and women with IGT, who may therefore be at increased risk of future development of NIDDM and CHD. [Diabetologia (1994) 37: 524–532]

Key words Impaired glucose tolerance, lipids, insulin, C-peptide, fat distribution, insulin resistance syndrome.

Previous research has shown a high prevalence of both NIDDM and CHD among second-generation (Nisei) Japanese-American men and a high prevalence of NIDDM among Nisei women compared to native Japanese [1–5]. We have proposed that these observations reflect the propensity in Japanese Americans to develop the insulin resistance syndrome, defined as the clustering of insulin resistance, hyperinsulinaemia, obesity (especially central or visceral obesity), hypertension, hypertriglyceridaemia, and low HDL cholesterol [6–8]. The relationship of visceral obesity to the abnormalities of glucose and lipid metabolism have been previously reported [9–12]. Exeptions related to ethnicity have been reported, however, for certain features of this syndrome. For example, Saad et al. [13] have reported that plasma insulin levels and insulin resistance were related to blood pressure in Whites but not in Pima Indians or Blacks, although in another

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; CHD, coronary heart disease; IGT, impaired glucose tolerance; AUC, area under the curve; ANOVA, analysis of variance

study of young black men a direct relationship between insulin resistance and blood pressure was observed [14]. Fasting insulin has been reported to be significantly correlated with blood pressure independent of obesity and age in Japanese children [15]. Studies in other migrant Asian populations have also shown that central adiposity and insulin resistance are associated with NIDDM and cardiovascular risk [16]. It would therefore be informative to know whether the younger third generation (Sansei) have any of the metabolic and adipose risk factors associated with the insulin resistance syndrome and the relationship of these to glucose tolerance status.

Subjects, materials, and methods

The protocol for this research was reviewed by the Human Subjects Review Committee at the University of Washington and each subject gave informed and signed consent. Subjects were enrolled through a community-wide recruitment using a comprehensive mailing list and telephone directory that included nearly 95% of the Japanese-American population of King County, Washington. Sansei were defined as any Japanese person born in the continental United States of Nisei parents or of one Nisei parent and one Sansei parent. The strategy was to study approximately 10% of the Sansei population 34 years old or older who were non-diabetic, and 230 subjects (115 men, 115 women) were enrolled from among 533 volunteers (266 men, 267 women) who met the criteria for generation and age. Excluded were 151 men and 152 women for the following reasons: same gender as enrolled sibling (14 men, 21 women) or enrolled first cousin (23 men, 37 women), born and raised in Hawaii (29 men, 26 women), educated in Japan (3 men, 2 women), Nisei parents were educated in Japan (15 men, 11 women), moved out of King County (13 men, 4 women), adopted (1 man, 3 women), scheduling conflicts (22 men, 20 women), excess volunteers (23 men, 9 women), and confounding medical conditions (11 men, 19 women). These medical conditions were insulin-dependent diabetes mellitus or NIDDM (7 men, 3 women), cancer (2 men, 3 women), hepatitis (1 man), kidney disease (2 women), thyroid disease (2 women), lupus (1 woman), steroid-treated asthma (2 women), pregnancy (1 woman), pulmonary disease (1 woman), Epstein-Barr virus infection (1 woman), and refusal to discontinue nasal decongestants (1 man, 3 women).

Subjects were studied at the General Clinical Research Center, University of Washington Medical Center following an overnight 10-h fast. All subjects underwent a 75-g oral glucose tolerance test, and glucose tolerance was categorized according to the criteria of the World Health Organization [17]. Baseline blood samples were withdrawn for measurement of glucose, insulin, C-peptide, lipids, and lipoproteins. Subjects then ingested a solution of glucose (75 g) in water over approximately 1 min and blood samples were withdrawn at 30, 60, 120, and 180 min for measurement of plasma glucose, insulin, and C-peptide. AUC for insulin, C-peptide, and glucose were calculated using the trapezoidal rule.

Height was measured to the nearest tenth centimeter and weight to the nearest hundredth kilogram and BMI was calculated as weight (kg)/height^2 (m^2). Skinfold thickness (mm) was measured (Lange calipers) on the left side of the body at six anatomic sites: forearm, biceps, triceps, subscapula, abdomen (midway between the umbilicus and the most lateral point), and anterior thigh. A midaxillary site was measured only in men. Cross-sectional body fat areas (cm^2) were assessed by computed tomography. Single slices were obtained at three levels: thorax at the level of the nipples, abdomen at the level of the umbilicus, and left midthigh; areas of subcutaneous thoracic, abdominal, and thigh fat and of intra-abdominal fat within the confines of the transversalis fascia were calculated, as described previously [18].

Plasma glucose was measured by an automated glucose oxidase method at the University of Washington Medical Center, Clinical Chemistry Laboratory. Plasma insulin and C-peptide were measured by radioimmunoassay performed in the Radioimmunoassay Core of the Diabetes Endocrinology Research Center using primary antisera developed in the Core [19, 20]. All lipid and lipoprotein measurements were performed at the Northwest Lipid Research Laboratory, according to modified procedures of the Lipid Research Clinics [21]. Apoproteins A1 and B were determined by standardized radioimmunoassays [22].

Statistical analysis

All values are expressed as mean ± SEM. For variables with highly skewed distributions, geometric means are presented and statistical tests computed on logarithmic transformations. Risk factors were analysed using normal glucose tolerance and IGT as the categorical variable. Statistically significant differences between groups were analysed by applying the two-sample *t*-test; all tests were two-sided. Adjustments (BMI, height, weight, intra-abdominal fat, and age) were made by analysis of covariance. In some analyses, subjects were separated into tertiles of the independent variable of interest, with the upper tertile further divided into an upper and a lower half, and data were analysed by ANOVA with tests for linear, cubic, and quadratic trends. Glucose, insulin, and C-peptide values during the oral glucose tolerance test were analysed by repeated measures ANOVA.

Results

Clinical characteristics: the mean age and age range were virtually identical between Sansei men and women (mean, 40.2 ± 0.4 years and range, 34.0–51.3 years, and mean, 40.1 ± 0.4 and range, 34.0–53.1 years, respectively). Among the men, 93 had normal glucose tolerance and 22 (19.1%) had IGT, while 79 women had normal glucose tolerance and 36 (31.3%) had IGT. The mean age of men with IGT (42.0 ± 1.1 years) was significantly greater than that of men with normal glucose tolerance (39.6 ± 0.4 years, $p = 0.049$), whereas the mean age of women with IGT (39.8 ± 0.5 years) was not significantly different from that of women with normal glucose tolerance (40.8 ± 0.7 years, $p = 0.25$).

Adiposity and body fat distribution by glucose tolerance status and gender: data concerning mean BMI, skinfolds, and body fat areas by computed tomography are summarized in Table 1. Men with IGT had greater mean BMI than men with normal glucose tolerance. After adjustment for BMI, only the computed tomography measurements of subcutaneous thoracic and intra-abdominal fat remained significantly different

Table 1. BMI and body fat distribution by glucose tolerance status (normal and IGT) and gender

	Men			Women		
	Normal ($n = 93$)	IGT ($n = 22$)	p-value	Normal ($n = 79$)	IGT ($n = 36$)	p-value
BMI (kg/m^2)	24.5 ± 0.3	26.8 ± 0.9	0.021	22.5 ± 0.3	23.3 ± 0.7	0.28
Skinfolds (mm):						
Forearm[a]	4.9 ± 0.2	5.8 ± 0.6	0.56	7.9 ± 0.4	8.6 ± 1.1	0.87
Biceps[a]	7.5 ± 0.5	11.0 ± 2.0	0.060	13.5 ± 0.9	15.5 ± 1.4	0.20
Triceps[a]	12.1 ± 0.6	15.9 ± 2.0	0.027	21.8 ± 0.9	23.3 ± 1.3	0.29
Subscapula	20.6 ± 0.9	27.8 ± 2.2	0.001	21.0 ± 1.3	25.0 ± 2.2	0.10
Chest	28.7 ± 1.3[b]	34.8 ± 3.0	0.049			
Abdomen	26.9 ± 1.2	34.2 ± 3.0	0.012	31.1 ± 1.2	34.1 ± 2.4	0.27
Thigh	22.3 ± 1.6	30.3 ± 3.8	0.037	45.0 ± 1.3	45.3 ± 1.3	0.86
Computed tomography fat area (cm^2):						
Thoracic subcutaneous	70.8 ± 3.9	113.7 ± 13.3	0.005	88.4 ± 7.6	123.7 ± 16.2	0.027
Abdominal subcutaneous	135.4 ± 7.2	184.2 ± 17.8	0.005	152.7 ± 8.7	175.8 ± 16.3	0.18
Intra-abdominal[a]	67.8 ± 3.7	104.1 ± 11.8	0.006	37.6 ± 2.5	57.7 ± 7.4	0.008
Thigh subcutaneous	48.3 ± 2.2	56.4 ± 5.5	0.13	94.0 ± 3.9	95.1 ± 6.8	0.88

[a] Statistical tests computed on logarithmic transformation
[b] $n = 90$ due to missing values in three subjects
Values are shown as mean ± SEM

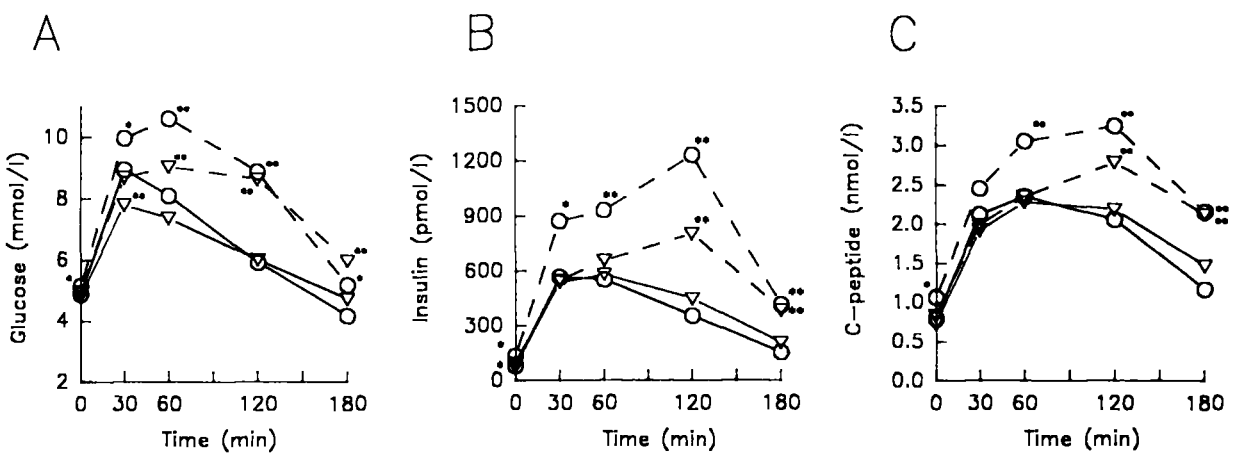

Fig. 1A–C. Plasma glucose (**A**), insulin (**B**), and C-peptide (**C**) levels during a 3-h 75-g oral glucose tolerance test for men (○) and women (▽) with normal glucose tolerance (—) and IGT (---). * $p < 0.05$, ** $p < 0.001$ for comparisons between normal glucose tolerance and IGT within each gender

between glucose tolerance groups ($p = 0.014$ and $p = 0.024$, respectively).

By contrast, the mean BMI of women did not differ significantly by glucose tolerance category. Significant differences in subcutaneous thoracic fat and intra-abdominal fat by computed tomography remained, after adjustment for BMI in both women and men ($p = 0.018$ and $p = 0.013$, respectively).

Insulin, C-peptide, and glucose levels by glucose tolerance status and gender (Fig. 1): both fasting insulin ($p = 0.004$) and fasting C-peptide levels ($p < 0.001$) were much higher in men with IGT than those with normal glucose tolerance. Differences were no longer significant, however, after simultaneous adjustment for age, BMI, and intra-abdominal fat ($p = 0.095$ for insulin and $p = 0.21$ for C-peptide). The greatest effect upon the p-value was observed with adjustment for intra-abdominal fat. Fasting insulin was also significantly higher in women with IGT than those with normal glucose tolerance ($p = 0.027$), and again the difference did not remain significant after simultaneous adjustment for age, BMI, and intra-abdominal fat ($p = 0.39$). This effect was mainly attributable to intra-abdominal fat. Fasting C-peptide levels did not differ significantly between women with IGT and those with normal glucose tolerance ($p = 0.12$).

The peak insulin and C-peptide levels were delayed and higher in men and women with IGT than in those with normal glucose tolerance (repeated measures ANOVA: $p < 0.001$ for insulin by glucose tolerance status in men and $p = 0.027$ in women, $p < 0.001$ for C-peptide by glucose tolerance status in men and women, $p < 0.001$ for interaction between glucose tolerance status and sample time for both insulin and C-peptide

Table 2. Fasting plasma lipids, lipoproteins, and apoproteins by glucose tolerance status (normal and IGT) and gender

	Men			Women		
	Normal ($n = 93$)	IGT ($n = 22$)	p-value	Normal ($n = 79$)	IGT ($n = 36$)	p-value
Cholesterol (mmol/l):						
Total	5.64 ± 0.09	5.80 ± 0.25	0.55	5.17 ± 0.08	5.33 ± 0.16	0.40
LDL	3.60 ± 0.09	3.47 ± 0.18	0.51	3.00 ± 0.06	3.25 ± 0.12	0.073
HDL	1.37 ± 0.04	1.23 ± 0.07	0.066	1.75 ± 0.05	1.56 ± 0.06	0.048
Triglycerides (mmol/l)[a]	1.64 ± 0.16	2.95 ± 0.73	0.079	1.05 ± 0.09	1.41 ± 0.24	0.055
Apoproteins (mg/dl):						
Apo-A1	141 ± 3	132 ± 4	0.11	155 ± 3	152 ± 5	0.60
Apo-B	110 ± 3	110 ± 4	0.93	91 ± 2	98 ± 4	0.078

[a] Statistical tests computed on logarithmic transformations
Values are shown as mean ± SEM

Table 3. Metabolic variables by intra-abdominal fat area tertiles in men

	Lower third ($n = 38$)	Middle third ($n = 39$)	Upper third, lower half ($n = 19$)	Upper third, upper half ($n = 19$)	p-value	p-value (linear trend)[a]	p-value (adjusted for BMI, weight, height)
Fasting insulin[b] (pmol/l)	56.2 ± 4.0 (62.8)[c]	80.4 ± 5.2 (81.4)	83.7 ± 8.5 (82.4)	138.5 ± 17.8 (124.4)	< 0.0001	< 0.0001 C:0.029	< 0.001
Insulin AUC[b] (nmol/l × min)	45.7 ± 3.1 (48.7)	71.7 ± 5.7 (72.2)	72.4 ± 19.7 (71.8)	139.2 ± 24.7 (130.9)	< 0.0001	< 0.0001	< 0.001
Fasting C-peptide[b] (nmol/l)	0.66 ± 0.03 (0.72)	0.81 ± 0.04 (0.82)	0.85 ± 0.05 (0.84)	1.10 ± 0.08 (1.01)	< 0.0001	< 0.0001 C:0.014	0.001
C-peptide AUC[b] (nmol/l × min)	303 ± 9 (313)	353 ± 16 (355)	363 ± 17 (362)	471 ± 34 (456)	< 0.0001	< 0.0001	< 0.001
Fasting glucose (mmol/l)	4.86 ± 0.08 (4.94)	4.98 ± 0.08 (4.99)	5.14 ± 0.11 (5.13)	5.27 ± 0.10 (5.18)	0.019	0.0017	0.38
2-h glucose (mmol/l)	6.36 ± 0.26 (6.32)	6.22 ± 0.26 (6.24)	7.27 ± 0.38 (7.29)	7.36 ± 0.40 (7.38)	0.022	0.0085	0.039
Glucose AUC (mmol/l × min)	1219 ± 34 (1214)	1241 ± 34 (1245)	1367 ± 54 (1369)	1374 ± 41 (1374)	0.012	0.0020	0.032
Total cholesterol (mmol/l)	5.60 ± 0.15 (5.51)	5.38 ± 0.12 (5.39)	6.18 ± 0.24 (6.20)	6.07 ± 0.24 (6.13)	0.0040	0.0096 C:0.016	0.003
LDL-cholesterol (mmol/l)	3.43 ± 0.12 (3.34)	3.40 ± 0.11 (3.39)	4.00 ± 0.23 (4.01)	3.92 ± 0.22 (4.00)	0.011	0.0050	0.005
HDL-cholesterol (mmol/l)	1.55 ± 0.06 (1.46)	1.34 ± 0.05 (1.34)	1.23 ± 0.06 (1.24)	1.10 ± 0.03 (1.18)	< 0.0001	< 0.0001	0.024
Triglycerides[b] (mmol/l)	2.70 ± 0.37 (3.07)	3.19 ± 0.76 (3.26)	3.93 ± 1.8 (3.87)	4.60 ± 0.91 (4.01)	0.015	0.0013	0.47
Apoprotein A-1 (mg/dl)	150.1 ± 4.8 (144.6)	135.6 ± 3.4) (135.8)	136.3 ± 4.6 (137.2)	127.6 ± 4.0 (132.0)	0.0046	0.0010	0.34
Apoprotein B (mg/dl)	102.7 ± 3.2 (102.1)	105.1 ± 3.3 (105.1)	118.5 ± 5.7 (118.6)	124.3 ± 5.8 (124.8)	0.0012	0.0001	0.005

[a] Trend is linear unless indicated (C: cubic)
[b] Geometric means are presented and statistics are computed on natural logarithms
[c] Mean adjusted for BMI, weight, and height is shown in parentheses
Values are shown as mean ± SEM

in men and women). The differences in insulin and C-peptide levels by glucose tolerance status remained significant after adjusting for age, BMI, and intra-abdominal fat in men. Differences in insulin levels by glucose tolerance status were, however, not significant ($p = 0.33$) in women after adjusting for age, BMI, and intra-abdominal fat, while differences in C-peptide levels by glucose tolerance status remained significant ($p = 0.021$). In general, men with IGT tended to have higher insulin and C-peptide levels than women with

Table 4. Metabolic variables by intra-abdominal fat area tertiles in women

	Lower third ($n = 38$)	Middle third ($n = 39$)	Upper third, lower half ($n = 19$)	Upper third, upper half ($n = 19$)	p-value	p-value (linear trend)[a]	p-value (adjusted for BMI, weight, height)
Fasting insulin[b] (pmol/l)	57.4 ± 5.2 (65.5)[c]	60.6 ± 2.8 (64.8)	88.6 ± 9.5 (85.3)	127.5 ± 15.6 (108.1)	< 0.0001	< 0.0001 Q:0.040	0.015
Insulin AUC[b] (nmol/l × min)	60.7 ± 4.1 (61.1)	63.8 ± 3.5 (63.3)	87.1 ± 10.0 (88.2)	130.4 ± 28.4 (128.8)	< 0.0001	< 0.0001 Q:0.0057	< 0.001
Fasting C-peptide[b] (nmol/l)	0.63 ± 0.03 (0.66)	0.67 ± 0.02 (0.68)	0.89 ± 0.05 (0.88)	1.00 ± 0.07 (0.94)	< 0.0001	< 0.0001	< 0.001
C-peptide AUC[b] (nmol/l × min)	316 ± 11 (308)	343 ± 9 (335)	384 ± 14 (392)	451 ± 28 (464)	< 0.0001	< 0.0001	< 0.001
Fasting glucose (mmol/l)	4.80 ± 0.07 (4.89)	4.82 ± 0.07 (4.87)	5.21 ± 0.16 (5.20)	5.16 ± 0.13 (5.03)	< 0.0001	0.0010	0.16
2-h glucose (mmol/l)	6.49 ± 0.24 (6.49)	6.87 ± 0.24 (6.86)	7.00 ± 0.31 (7.05)	8.00 ± 0.36 (7.96)	0.0053	0.0008	0.11
Glucose AUC (mmol/l × min)	1169 ± 33 (1168)	1237 ± 38 (1232)[c]	1311 ± 51 (1322)	1409 ± 45 (1403)	0.0012	< 0.0001	0.046
Total cholesterol (mmol/l)	4.97 ± 0.12 (5.07)	5.29 ± 0.11 (5.34)	5.31 ± 0.19 (5.31)	5.68 ± 0.22 (5.52)	0.016	0.0022	0.42
LDL-cholesterol (mmol/l)	2.79 ± 0.08 (2.81)	3.10 ± 0.09 (3.11)	3.29 ± 0.17 (3.31)	3.48 ± 0.15 (3.44)	0.0003	< 0.0001	0.024
HDL-cholesterol (mmol/l)	1.88 ± 0.06 (1.94)	1.81 ± 0.06 (1.83)	1.48 ± 0.09 (1.47)	1.36 ± 0.06 (1.29)	< 0.0001	< 0.0001	< 0.001
Triglycerides[b] (mmol/l)	1.66 ± 0.11 (1.66)	2.12 ± 0.19 (2.13)	2.67 ± 0.47 (2.70)	3.49 ± 1.06 (3.44)	< 0.0001	< 0.0001	0.002
Apoprotein A-1 (mg/dl)	160.3 ± 4.2 (163.3)	161.7 ± 3.8 (162.8)	138.0 ± 5.0 (137.7)	141.9 ± 5.7 (138.1)	0.0005	0.0005 C:0.017	0.003
Apoprotein B (mg/dl)	84.0 ± 2.7 (83.0)	92.5 ± 2.7 (92.1)	100.7 ± 5.8 (101.3)	106.5 ± 5.1 (107.2)	0.0003	< 0.0001	0.010

[a] Trend is linear unless indicated (C: cubic or Q: quadratic)
[b] Geometric means are presented and statistics are computed on natural logarithms
[c] Mean adjusted for BMI, weight, and height is shown in parentheses
Values are shown as mean ± SEM

IGT ($p < 0.005$ for both insulin and C-peptide for interaction between glucose tolerance status and gender).

Lipids and lipoproteins by glucose tolerance status and gender: mean fasting lipids, lipoproteins, and apoproteins are shown in Table 2. Both normal glucose tolerant and IGT men had more atherogenic profiles than women. Within each gender, however, normal glucose tolerant and IGT subjects did not differ significantly although those with IGT tended to have higher triglyceride and lower HDL cholesterol levels (for women the difference in HDL cholesterol was significant, $p = 0.048$). In addition, women with IGT tended to have higher LDL cholesterol and apoprotein B levels than did women with normal glucose tolerance. For all of these tendencies, p-values increased to more than 0.10 after simultaneously adjusting for age, BMI, and intra-abdominal fat, and the greatest effect upon the p-value was seen with adjustment for intra-abdominal fat.

Relationship of adiposity to metabolic variables: men and women were separately divided into tertiles of several selected adiposity variables: BMI, as a measurement of general adiposity, and intra-abdominal fat area, thoracic subcutaneous fat area, abdominal subcutaneous fat area, and subscapular skinfold thickness as measurements of central adiposity. The uppermost tertile was further subdivided into a lower and an upper half. Mean values were calculated for insulin (fasting and AUC), C-peptide (fasting and AUC), glucose (fasting, 2-h, and AUC), cholesterol (total, LDL, and HDL), triglycerides, apoprotein A-1, and apoprotein B. The results with respect to intra-abdominal fat are shown in Table 3 for men and Table 4 for women.

All of the metabolic variables showed a significant relationship to intra-abdominal fat in both men and women. For all variables except fasting glucose, triglycerides, and apoprotein A-1 in men and fasting glucose, 2-h glucose, and total cholesterol in women, the relationships remained significant after adjusting for BMI, weight, and height.

Several metabolic variables were not significantly associated with the other adiposity variables. These

Table 5. Glucose, lipids, and lipoproteins by fasting insulin tertiles in men and women

	Lower third	Middle third	Upper third, lower half	Upper third, upper half	*p*-value	*p*-value (linear trend)[a]
Men	n = 43	*n* = 33	*n* = 19	*n* = 20		
Fasting glucose (mmol/l)	4.87 ± 0.07	4.86 ± 0.08	5.16 ± 0.09	5.44 ± 0.10	< 0.0001	< 0.0001
2-h glucose (mmol/l)	6.62 ± 0.17	5.94 ± 0.27	6.52 ± 0.29	7.89 ± 0.40	0.0006	0.012 Q:0.0008
Glucose AUC (mmol/l × min)	1251 ± 36	1193 ± 36	1299 ± 32	1449 ± 37	0.0002	0.0007 Q:0.0049
Total cholesterol (mmol/l)	5.60 ± 0.14	5.60 ± 0.15	5.93 ± 0.24	5.83 ± 0.24	0.51	
LDL-cholesterol (mmol/l)	3.48 ± 0.12	3.66 ± 0.14	3.80 ± 0.21	3.51 ± 0.20	0.52	
HDL-cholesterol (mmol/l)	1.51 ± 0.06	1.37 ± 0.04	1.18 ± 0.04	1.13 ± 0.06	< 0.0001	< 0.0001
Triglycerides (mmol/l)	2.75 ± 0.25	2.88 ± 0.34	4.21 ± 0.67	5.00 ± 2.19	0.0009	0.0001
Apoprotein A-1 (mg/dl)	148.8 ± 4.2	140.8 ± 3.8	136.5 ± 4.5	122.6 ± 4.3	0.0030	0.0003
Apoprotein B (mg/dl)	105.5 ± 4.1	111.6 ± 5.9	116.3 ± 5.0	109.1 ± 5.0	0.37	
Women	n = 38	*n* = 33	*n* = 23	*n* = 20		
Fasting glucose (mmol/l)	4.70 ± 0.07	4.88 ± 0.08	5.09 ± 0.11	5.28 ± 0.12	0.0002	< 0.0001
2-h glucose (mmol/l)	6.66 ± 0.22	6.56 ± 0.23	7.25 ± 0.37	7.80 ± 0.36	0.015	0.0037
Glucose AUC (mmol/l × min)	1180 ± 30	1225 ± 38	1292 ± 57	1381 ± 48	0.0089	0.0008
Total cholesterol (mmol/l)	5.05 ± 0.11	5.18 ± 0.13	5.51 ± 0.20	5.43 ± 0.20	0.11	
LDL-cholesterol (mmol/l)	2.89 ± 0.08	3.04 ± 0.10	3.33 ± 0.16	3.26 ± 0.15	0.028	0.0055
HDL-cholesterol (mmol/l)	1.84 ± 0.07	1.72 ± 0.06	1.67 ± 0.10	1.48 ± 0.08	0.014	0.0015
Triglycerides (mmol/l)	1.73 ± 0.09	2.10 ± 0.30	2.60 ± 0.33	3.09 ± 1.02	0.0004	< 0.0001
Apoprotein A-1 (mg/dl)	158.0 ± 4.0	154.1 ± 3.9	156.4 ± 7.0	144.9 ± 5.6	0.32	
Apoprotein B (mg/dl)	87.3 ± 2.7	91.2 ± 3.2	101.7 ± 5.5	98.2 ± 4.6	0.036	0.0098

[a] Trend is linear unless indicated (Q: quadratic).
Values are shown as mean ± SEM

data are not shown but the relationships that were not significant are summarized here. In men, total cholesterol and LDL cholesterol were not significantly related to BMI, thoracic subcutaneous fat, abdominal subcutaneous fat, and subscapular skinfold; triglycerides, apoprotein B, and 2-h glucose were not significantly related to subscapular skinfold; and glucose AUC was not significantly related to abdominal subcutaneous fat. In women, total cholesterol and apoprotein B were not significantly related to BMI and subscapular skinfold; apoprotein A-1 was not signficantly related to thoracic subcutaneous fat, abdominal subcutaneous fat, and subscapular skinfold; HDL-cholesterol was not significantly related to abdominal subcutaneous fat; and LDL-cholesterol was not significantly related to subscapular skinfold.

Relationship of fasting insulin and C-peptide to glucose, lipids, and lipoproteins: men and women were separately divided into tertiles of fasting insulin and C-peptide. The uppermost tertile was further subdivided into a lower half and an upper half. Mean values were calculated for glucose (fasting, 2-h, and AUC), cholesterol (total, LDL, and HDL), triglycerides, apoprotein A-1, and apoprotein B. The results with respect to fasting insulin are shown in Table 5 for men and women.

All variables, except for total cholesterol, LDL-cholesterol, and apoprotein B in men and total cholesterol and apoprotein A-1 in women, were significantly related to fasting insulin. The relationship of fasting C-peptide to these variables was similar in men. In women, however, total cholesterol ($p = 0.041$) and apoprotein A-1 ($p = 0.0046$) were also significantly related to fasting C-peptide.

Discussion

Cross-sectional [23–26] and prospective [27] studies in Nisei men have identified greater adiposity, including greater amounts of thoracic and intra-abdominal fat, higher fasting plasma insulin, C-peptide, and triglyceride levels, and lower fasting plasma HDL cholesterol levels as some of the risk factors associated in this population with NIDDM and CHD. There is now much evidence that obesity, especially increased deposition of fat in a truncal location, is associated with hyperinsulinaemia and with NIDDM [6–8, 27, 28]. It is

also clear that under certain conditions, fasting hyperinsulinaemia, measured as elevation of either insulin or C-peptide, reflects the presence of insulin resistance [29, 30]. Although the prevalence of hyperinsulinaemia is increased in the non-diabetic members of populations with a high prevalence of NIDDM [29, 31] and insulin resistance is an early abnormality in subjects destined to develop NIDDM [27, 32–35], decompensation to NIDDM in insulin-resistant individuals may be prevented by the secretion of more insulin [36]. The resultant hyperinsulinaemia, however, may have adverse cardiovascular consequences [37–40].

The presence of IGT may be associated with increased risk of NIDDM, CHD, and hypertension [41–47], and our results suggest that many Sansei men with IGT have begun to accumulate truncal and visceral fat and exhibit insulin resistance. Although Sansei women with IGT also had more truncal and intra-abdominal fat and higher fasting insulin levels than did women with normal glucose tolerance, levels were not as high as in Sansei men. It may be that the premenopausal status of the vast majority of the Sansei women in this sample is important. Indirect evidence in support of this conclusion is provided by the observation that Nisei women, the vast majority of whom are postmenopausal, have proportionally more intra-abdominal and thoracic subcutaneous fat and less thigh subcutaneous fat than do Sansei women [48]. It is also possible that for Sansei women, IGT may have been over-diagnosed because of the emphasis placed on the 120-min plasma glucose level. This possibility is suggested by the observation that the 30-min and the 60-min plasma glucose levels in women with IGT were much lower than in men with IGT.

In contrast to the marked differences in BMI, pattern of body fat distribution, and fasting insulin and C-peptide levels between normal and IGT men, there were no significant lipid, lipoprotein, or apoprotein differences, although IGT men tended to have lower HDL cholesterol and higher triglyceride. IGT seemed to be more strongly associated with an atherogenic lipid profile among women, with significantly lower HDL cholesterol whereas triglyceride and LDL cholesterol both tended to be slightly higher. Analyses by tertiles of BMI or body fat distribution, however, showed significant relationships of all of the metabolic variables with intra-abdominal fat in both men and women as well as significant relationships for most of the metabolic variables with BMI, thoracic subcutaneous fat, abdominal subcutaneous fat, and subscapular skinfold. Furthermore, although Sansei women with IGT had lower fasting insulin levels than men with IGT, analyses by tertiles of fasting insulin and C-peptide, both of which were used as surrogate markers of insulin resistance, showed a significant relationship to glucose and most of the lipid and lipoprotein variables in both men and women. These results suggest that significant adverse changes in the metabolic variables are generally associated with adiposity, particularly with visceral adiposity, and with insulin resistance in both men and women, but that an association of these metabolic changes with glucose intolerance may require more severe glucose intolerance (e.g. diabetes). These possibilities may be clarified by prospective studies.

We have previously shown that when Nisei men and women are subdivided into either android or gynoid subsamples based upon distribution of subcutaneous fat, differences in intra-abdominal fat, and the fasting plasma levels of insulin, C-peptide, triglyceride, and HDL cholesterol between the fat pattern groups were highly significant for women but not for men. These observations suggest that in Nisei women but not in men, the android pattern of subcutaneous fat distribution is significantly related to greater metabolic and atherogenic risks [26]. We have also shown in a general linear model that the contributions of diabetic status (normal vs NIDDM) and intra-abdominal fat to potentially atherogenic variables (fasting insulin, triglyceride, and HDL cholesterol levels) differ between Nisei men and women [25]. For women, diabetic status did not substantially improve the model once intra-abdominal fat had been entered. By contrast in men, diabetic status remained a significant predictor for the metabolic variables even after intra-abdominal fat was considered in the model. Future prospective studies in Sansei women may show whether metabolic risk factors increase significantly at the time of menopause when truncal and visceral adiposity also increase.

In conclusion, metabolic and adipose risk factors associated with the insulin resistance syndrome are identifiable among Sansei men and women with IGT, who may therefore be at increased risk of developing NIDDM and CHD. Among women, fasting insulin and visceral adiposity were not as increased as in men. Whether this finding is due to their premenopausal hormonal status may be elucidated by prospective studies.

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