Insulin Secretion and Sensitivity in Non-obese and Obese Japanese Patients With Coronary Artery Disease

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In a cross-sectional study of 240 patients with angiographically documented coronary artery disease (CAD), we investigated whether obese and non-obese subjects differed as to the influence of insulin deficiency and insulin resistance on glucose intolerance and cardiovascular risk. Patients were classified according to a 75-g oral glucose tolerance test as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes mellitus (DM). We defined obesity as a body mass index (BMI) exceeding 25 kg/m^2. Early phase insulin secretion (insulinogenic index) declined with worsening glucose intolerance in non-obese ($\tau = -.216$, $P < .001$; Kendall's correlation coefficient) and obese subjects ($\tau = -.392$, $P < .001$). Total insulin secretion was higher in obese subjects with NGT or IGT than in controls and decreased in association with worsening glucose intolerance in obese subjects ($\tau = -.239$, $P < .001$). Insulin sensitivity was calculated by 3 proposed indices. The first of these decreased in association with worsening in glucose tolerance in non-obese subjects ($\tau = -.137$, $P < .01$). The second showed such a pattern in both groups (non-obese, $\tau = -.407$, $P < .001$; obese, $\tau = -.311$, $P < .001$), as did the third (non-obese, $\tau = -.512$, $P < .001$; obese, $\tau = -.488$, $P < 0.001$). Because even prediabetic Japanese subjects with CAD showed a latent insulin secretion defect in response to a glucose load, as well as impaired insulin sensitivity, compensatory hyperinsulinemia is not a sensitive indicator of coronary risk.

SEVERAL STUDIES HAVE confirmed that hyperinsulinemia, which is frequently associated with glucose intolerance and obesity, is also associated with cardiovascular risk.[1-3] However, relationships between metabolic abnormalities may differ between Caucasian and Japanese subjects,[4] because the Japanese population is relatively lean.[5] In a Caucasian population, decreased insulin sensitivity has been reported to be a common physiologic defect underlying type 2 diabetes and glucose intolerance, while possibly contributing to hypertension, dyslipidemia, and risk for coronary artery disease (CAD).[6] On the other hand, in a Japanese population, insulin secretion in patients with type 2 diabetes mellitus was characterized by a decrease in the early-phase response to glucose,[7] suggesting impaired insulin secretion rather than impaired insulin sensitivity as the major cause of glucose intolerance.[8] While insulin sensitivity can be measured by the euglycemic hyperinsulinemic clamp technique,[9] this method is invasive and technically difficult. While homeostasis model assessment (HOMA) probably represents the most simple index for evaluating insulin sensitivity, particularly in epidemiologic studies,[10] drawbacks for clinical application have been reported. Alternatively, oral glucose tolerance tests have been performed to evaluate glucose intolerance and insulin secretion. The validity of insulin sensitivity indices based on this test had not been confirmed until recently, when 3 teams of investigators[11-13] demonstrated that an individual's insulin sensitivity can be predicted with formules from plasma glucose and insulin concentrations obtained during a glucose tolerance test. Insulin sensitivity calculated with each reported formula correlated well with euglycemic hyperinsulinemic clamp results. The present study was performed to determine whether Japanese subjects with CAD show impaired insulin secretion in response to an oral glucose load or impaired insulin sensitivity.

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SUBJECTS AND METHODS

Patients

Between April 1997 and March 2000, 354 consecutive Japanese patients underwent diagnostic cardiac catheterization, including coronary angiography, as part of an evaluation for chest pain, electrocardiographic abnormalities, or an abnormal stress test. Of these, 240 patients (189 men and 51 women; mean age, 63.6 years; range, 35 to 84) were considered for analysis in accordance with the following criteria: organic coronary artery stenosis of ≥75% of the luminal diameter in at least 1 coronary artery and performance of a 75-g oral glucose tolerance test. Patients with a previous history of overt diabetes or treatment with oral antidiabetic drugs or insulin were excluded. Patients with signs of congestive heart failure, chronic infectious diseases, renal failure, liver disease or cancer, and those with a prior gastrectomy were also excluded. None received drugs affecting plasma glucose concentration or insulin sensitivity. Fifty non-obese Japanese subjects with normal glucose tolerance and no history of CAD served as a control group. This study was conducted in accordance with the Helsinki Declaration, and written informed consent was obtained from all subjects.

Oral Glucose Tolerance Test

A standard 75-g oral glucose tolerance test was performed after patients had resumed unrestricted activity, waiting at least 2 weeks after any coronary episode to avoid transient influences on insulin sensitivity. Plasma samples were obtained at 0, 30, 60, 90, 120, and 180 minutes after the glucose load. Plasma glucose was determined with an autoanalyzer using a glucose oxidase method, and immunoreactive insulin was measured by enzyme immunoassay (Entym Insulin test; Roche, Basel, Switzerland). Glucose tolerance was classified into 3 categories based on the criteria currently proposed by the American Diabetes Association[14]: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes mellitus (DM).

Evaluation for Insulin Secretion

Insulinogenic index, a widely used index of early-phase insulin response, was defined as the ratio of the increment of immunoreactive

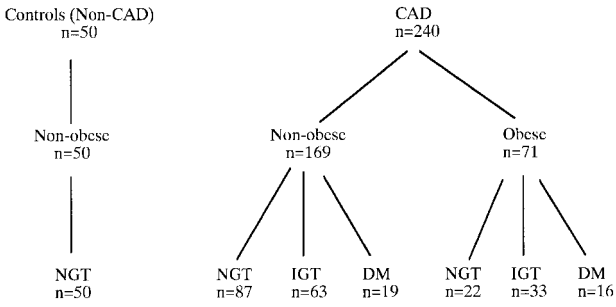

Fig 1. Flow chart of the subgroup structure. CAD, coronary artery disease; NGT, normal glucose tolerance IGT, impaired glucose tolerance; DM, type 2 diabetes mellitus.

insulin to that of plasma glucose at 30 minutes after glucose loading.[7] To assess total insulin secretion, area under the plasma insulin response curve was calculated from fasting, 30-minute, 60-minute, 120-minute, and 180-minute plasma insulin concentrations using the trapezoid rule.[15]

Insulin Sensitivity Index

Insulin sensitivity was assessed as an insulin sensitivity index (ISI) calculated using glucose tolerance test values by 3 previously proposed formulas. The index as proposed by Matsuda and DeFronzo[11] was calculated as follows: ISI-M = 100,000/square root of [PG(0-min) × IRI(0-min)] × [PG(mean) × IRI(mean)], in which the means were calculated from concentrations throughout the glucose tolerance test.

The second formula used was proposed by Stumvoll et al.[12] ISI-S = 0.226 − 0.0032 × BMI − 0.0000645 × IRI(120-min) − 0.00375 × PG(90-min).

The third formula used was proposed by Gutt et al.[13] ISI-G = *m*/[PG(0-min) + PG(120-min)] × 0.5/log [IRI(0-min) + IRI(120-min) × 0.5] in which *m* is the glucose uptake rate in peripheral tissues, calculated as *m* = [75,000 mg + [PG(0-min) − PG(120-min)] × 0.19 × BW]/120 min.

Statistical Analysis

Values are presented as the mean ± SD. Diffences between controls and each subgroup were tested with Student's *t* test. Differences among subgroups were tested with analysis of variance (ANOVA) followed by the Scheffe's test. Furthermore, Kendall's correlation coefficient (τ value) was used to evaluate the relationships between variables and the degree of glucose tolerance (NGT, IGT, and DM). Differences were considered significant when $P < .05$.

RESULTS

Patients' profile

Patients were classified as obese (body mass index [BMI] ≥ 25 kg/m^2, n = 71) or non-obese (n = 169). Both groups were subdivided according to the results of glucose tolerance test: NGT, IGT, and DM. As a result, patients were divided into 6 groups: non-obese-NGT (n = 87), non-obese-IGT (n = 63), non-obese-DM (n = 19), obese-NGT (n = 22), obese-IGT (n = 33), and obese-DM (n = 16). Flow chart of the subgroup structure is shown in Fig 1.

As shown in the Table 1, no significant differences were seen between groups with respect to mean age, systolic and diastolic blood pressure, or serum concentration of total cholesterol. Serum concentration of triglycerides was significantly higher in non-obese-DM than in non-obese-IGT. Fasting plasma glucose was significantly higher in non-obese-IGT, non-obese-DM, obese-IGT, and obese-DM than in controls. Fasting plasma glucose was also significantly higher in non-obese-DM than in non-obese-NGT and non-obese-IGT; the same pattern prevailed among obese subjects. Fasting immunoreactive insulin was significantly higher in obese-subjects with NGT, IGT, and DM than in controls.

Insulin Secretion

With respect to the insulinogenic index, no significant differences were seen between controls (n = 50, 0.56 ± 0.42) and all CAD (n = 240, 0.64 ± 0.55), and no significant differences among controls, non-obese-CAD (n = 169, 0.63 ± 0.54), and obese-CAD (n = 71, 0.65 ± 0.58). The insulinogenic index was significantly higher in non-obese-NGT and obese-NGT than in controls, while being significantly lower in non-obese-DM and obese-DM than in controls (Fig 2). The insuli-

Table 1. Subjects Characteristics

	Control	Nonobese			Obese		
		NGT	IGT	DM	NGT	IGT	DM
No.	50	87	63	19	22	33	16
Age (yr)	60.6 ± 12.3	63.7 ± 10.1	66.8 ± 9.0	65.4 ± 9.4	58.1 ± 10.9	59.9 ± 11.0	58.2 ± 9.0
BMI (kg/m^2)	22.1 ± 2.2	21.7 ± 2.2	22.2 ± 2.0	23.2 ± 1.5	27.0 ± 2.0*	27.4 ± 3.3*	28.3 ± 4.2*
SBP (mm Hg)	135 ± 20	125 ± 20	127 ± 23	129 ± 21	121 ± 16	125 ± 22	129 ± 19
DBP (mm Hg)	78 ± 15	72 ± 13	70 ± 13	74 ± 11	71 ± 12	74 ± 13	74 ± 12
TC (mmol/L)	5.25 ± 1.02	4.98 ± 1.10	4.99 ± 1.03	5.04 ± 1.52	4.92 ± 0.91	5.25 ± 1.03	5.32 ± 1.08
TG (mmol/L)	1.28 ± 0.63	1.23 ± 0.74	1.04 ± 0.59	1.55 ± 1.13†	1.23 ± 0.64	1.24 ± 0.74	1.24 ± 0.75
FPG (mmol/L)	5.02 ± 0.38	5.07 ± 0.44	5.43 ± 0.49*‡	5.91 ± 1.02*‡§	5.13 ± 0.45	5.32 ± 0.52*	6.13 ± 0.66*‡§
FIRI (pmol/L)	38.9 ± 18.5	42.2 ± 26.6	43.1 ± 29.2	39.8 ± 20.1	54.6 ± 20.7‖	60.0 ± 39.1*	49.0 ± 24.2‖

NOTE. Data are mean ± SD.

Abbreviations: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, plasma total cholesterol; TG, plasma triglycerides; FPG, plasma fasting glucose; FIRI, plasma fasting insulin.

*$P < .01$ *v* control; †$P < .05$ *v* IGT; ‡$P < .01$ *v* NGT; §$P < .01$ *v* IGT; ‖$P < .05$ *v* control.

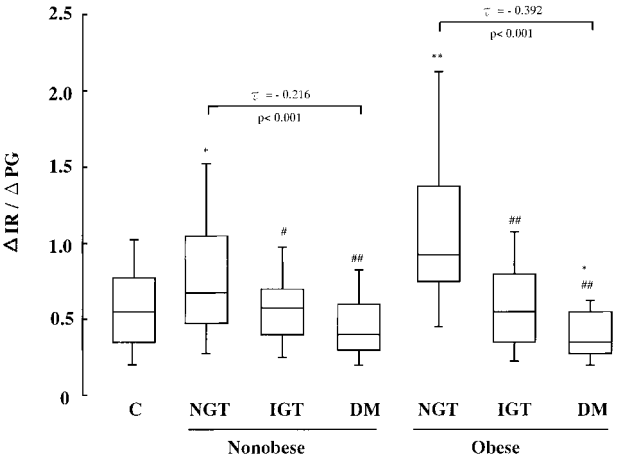

Fig 2. Early-phase insulin responses to OGTT (ΔIRI/ΔPG values) in non-obese and obese subjects subdivided according to glucose tolerance. Whisker plots showing the 10th, 25th, 50th, 75th, and 90th percentiles of distribution of ΔIRI/ΔPG values. *$P < .05$ *v* controls, **$P < .01$ *v* controls, #$P < .05$ *v* NGT, ##$P < .01$ *v* NGT.

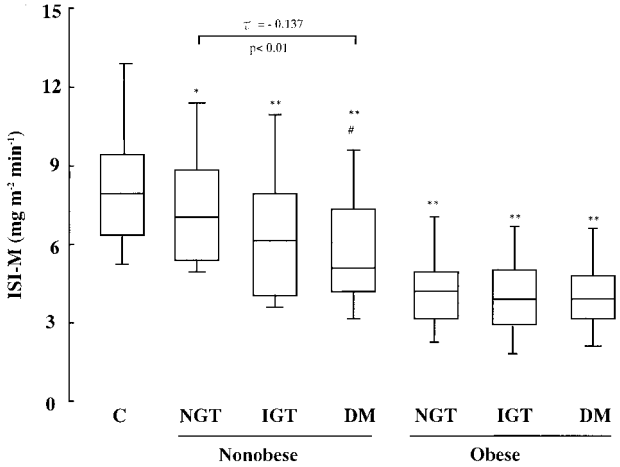

Fig 4. ISI-M in non-obese and obese subjects subdivided according to glucose tolerance. Whisker plots showing the 10th, 25th, 50th, 75th, and 90th percentiles of distribution of ISI-M values. *$P < .05$ *v* controls, **$P < .01$ *v* controls, #$P < .05$ *v* NGT.

nogenic index decreased significantly with worsening in glucose intolerance in both non-obese subjects ($\tau = -.216$, $P < .001$ by Kendall's correlation coefficient) and obese subjects ($\tau = -.392$, $P < .001$) (Fig 2).

Total insulin secretion during the test (AUC_{IRI}) was significantly higher in all CAD (n = 240, 594 ± 297 pmol·h^{-1}·L^{-1}) than in controls (n = 50, 474 ± 248), and was significantly higher in obese CAD (n = 71, 711 ± 367) than in controls and non-obese CAD (n = 169, 544 ± 247). The AUC_{IRI} was significantly higher in obese-NGT and obese-IGT than in controls (Fig 3). No correlation was seen between AUC_{IRI} and glucose tolerance in non-obese subjects ($\tau = .066$, $P = .214$ by Kendall's correlation coefficient), but AUC_{IRI} decreased significantly as glucose intolerance worsened in obese subjects ($\tau = -.239$, $P < .001$) (Fig 3).

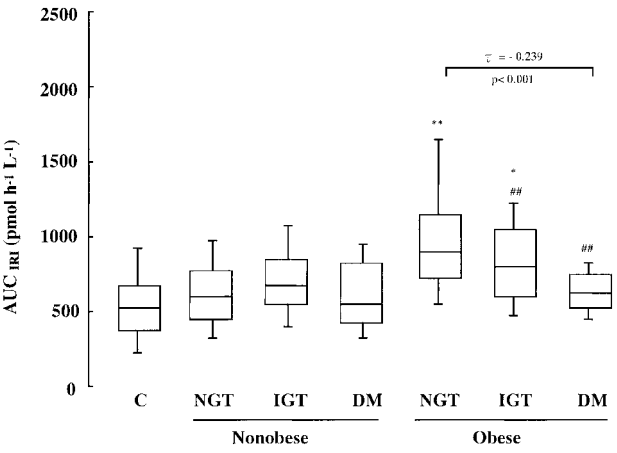

Fig 3. Total insulin responses to OGTT (AUC_{IRI} values) in non-obese and obese subjects subdivided according to glucose tolerance. Whisker plots showing the 10th, 25th, 50th, 75th, and 90th percentiles of distribution of AUC_{IRI} values. *$P < .05$ *v* controls, **$P < .01$ *v* controls, ##$P < .01$ *v* NGT.

Insulin Sensitivity

By Matsuda's formula, ISI-M was significantly lower in all CAD (n = 240, 5.91 ± 3.07 mg·m^{-2}·min^{-1}) than in controls (n = 50, 8.27 ± 4.56) and was significantly lower in obese CAD (n = 71, 4.46 ± 2.06) than in controls and non-obese CAD (n = 169, 6.51 ± 3.22). ISI-M was also significantly lower in both non-obese and obese subjects with all glucose tolerance categories than in controls (Fig 4). The index showed a significant decrease with worsening of glucose intolerance in non-obese subjects ($\tau = -.137$, $P < .01$ by Kendall's correlation coefficient), but not in obese subjects ($\tau = -.015$, $P = .857$) (Fig 4).

By Stumvoll's formula, ISI-S was significantly lower in all CAD (n = 240, 0.095 ± 0.025 μmol·kg^{-1}·min^{-1}·pmol^{-1}) than in controls (n = 50, 0.115 ± 0.013), and was significantly lower in obese CAD (n = 71, 0.075 ± 0.022) than in controls and non-obese CAD (n = 169, 0.103 ± 0.021). ISI-S was also significantly lower in non-obese subjects with IGT or DM and in obese subjects in all glucose tolerance categories than in controls (Fig 5). The index showed a significant decrease with worsening of glucose intolerance in both non-obese subjects ($\tau = -.407$, $P < .001$) and obese subjects ($\tau = -.311$, $P < .001$) (Fig 5).

By Gutt's formula, ISI-G was significantly lower in all CAD (n = 240, 65.8 ± 26.6 mg·L^2·mmol^{-1}·mU^{-1}·min^{-1}) than in controls (n = 50, 87.4 ± 21.8) and was significantly lower in obese CAD (n = 71, 55.1 ± 21.2) than in controls and non-obese CAD (n = 169, 70.3 ± 27.4). ISI-G also was significantly lower in non-obese subjects with IGT or DM and obese subjects with similar glucose tolerance than in controls (Fig 6). The index showed a significant decrease with worsening of glucose intolerance in both non-obese subjects ($\tau = -.512$, $P < .001$) and obese subjects ($\tau = -.488$, $P < .001$) (Fig 6).

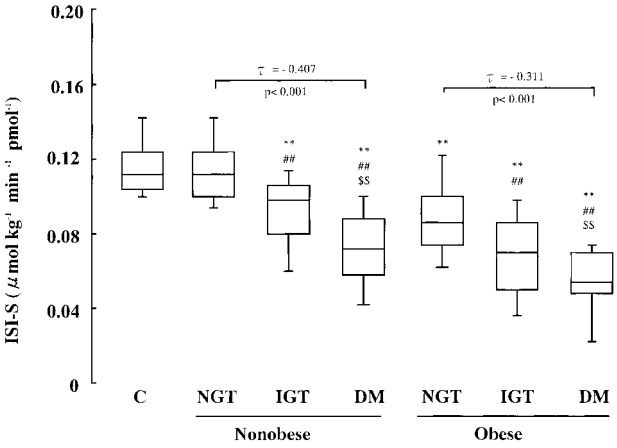

Fig 5. ISI-S in non-obese and obese subjects subdivided according to glucose tolerance. Whisker plots showing the 10th, 25th, 50th, 75th, and 90th percentiles of distribution of ISI-S values. *$P < .05$ *v* controls, **$P < .01$ *v* controls, ##$P < .01$ *v* NGT, $$$P < .01$ *v* IGT.

DISUCUSSION

In considering associations between glucose intolerance and CAD, the influence of obesity must be considered because this factor significantly affects both insulin secretion and insulin sensitivity. Caucasians, Pima Indians, and Mexican Americans show relatively high insulin responses to an oral glucose load; most Japanese subjects with glucose intolerance are less obese than in such other ethnic groups in which insulin resistance has been reported to play a central role in glucose intolerance. Therefore, relative contributions of insulin deficiency and insulin resistance to CAD in Japanese subjects remains a matter of controversy. While both defects are present in most Japanese subjects with established type 2 diabetes, we focused on newly diagnosed type 2 diabetes in defining our group with diabetic glucose tolerance patterns.

In cross-sectional studies, Caucasian subjects with IGT have been found to be more hyperinsulinemic than those with NGT.[16] The insulinogenic index (Δ IRI/Δ PG) has been reported to provide reliable indication of a latent defect in early insulin secretion in response to a glucose load.[17] In some studies of Japanese subjects, early-phase insulin responses to a glucose load were markedly decreased in subjects with IGT.[7,8,18] A decreased early response during an oral glucose tolerance test has also been found in Japanese Americans before the onset of diabetes.[19] Our study demonstrated that the insulinogenic index decreased significantly with worsening of glucose intolerance in both non-obese and obese subjects. When glucose tolerance was normal, only obese subjects had a significantly higher insulinogenic index than controls. These results suggested that most Japanese subjects with glucose intolerance have an impaired insulin response, which probably makes a predominant contribution to pathogenesis in most Japanese cases of type 2 diabetes. The overall insulin secretory response was also evaluated as the sum of immunoreactive insulin concentrations during the test; this overall insulin secretion was significantly higher in obese subjects with NGT or IGT than in controls. However, total immunoreactive insulin was similar between controls and non-obese subjects.

Although a large body of evidence has linked compensatory hyperinsulinemia to a cluster of coronary risk factors, no consensus has been reached as to whether insulin sensitivity contributes significantly to CAD.[20] The euglycemic hyperinsulinemic clamp method has been considered the best way to measure insulin sensitivity, but technical requirements and high cost have limited its use in clinical practice. HOMA, in which an index is caluculated from fasting insulin and fasting plasma glucose concentrations, represents the most simple method of evaluating insulin sensitivity, particularly in epidemiologic studies.[10] However, some reported limitations restrict its clinical use. Some investigators have reported a poor correlation of insulin sensitivity results between HOMA and the euglycemic clamp technique.[21] Simple, but reliable, methods for assessing insulin sensitivity are required. In this study, we used 3 insulin sensitivity indices based on glucose tolerance test results; these methods have been reported to agree well with the glucose clamp procedure.[11-13] We observed considerably impaired insulin sensitivity in non-obese-IGT, as well as obese subjects with NGT or IGT, while in contrast, we found no apparent differences in fasting serum insulin concentration or total immunoreactive insulin during the test between non-obese-IGT and controls. Therefore, in non-obese Japanese subjects, compensatory hyperinsulinemia apparently is not a reliable indicator of CAD, although in other ethic groups, much evidence has linked compensatory hyperinsulinemia to abnormalities that increase coronary risk of CAD.

Study limitations are the fact that this is a cross-sectional, but not prospective analysis, and we have no available data of Japanese American or Japanese-Western subjects. Further study will be needed to clarify the ethnic difference and environmental factors.

In summary, the present results demonstrate that Japanese subjects with angiographically documented CAD are characterized by a latent defect in insulin secretion in response to a glucose load, as well as impaired insulin sensitivity, even in the prediabetic state.

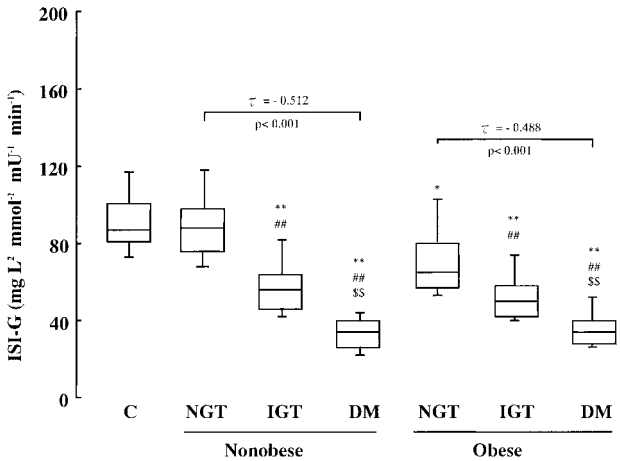

Fig 6. ISI-G in non-obese and obese subjects subdivided according to glucose tolerance. Whisker plots showing the 10th, 25th, 50th, 75th, and 90th percentiles of distribution of ISI-G values. **$P < .01$ *v* controls, ##$P < .01$ *v* NGT, $$$P < .01$ *v* IGT.

REFERENCES

1. Zavaroni I, Bonora E, Pagliara M, et al: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 320:702-706, 1989

2. Fontbonne A, Charles MA, Thibult N, et al: Hyperinsulinemia as a predictor of coronary heart disease mortality in a healthy population. Diabetologia 34:356-361, 1991

3. Despres JP, Lamarche B, Mauriege P, et al: Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 334:952-957, 1996

4. Saad MF, Lillioja S, Nyomba BL, et al: Racial differences in the relation between blood pressure and insulin resistance. N Engl J Med 324:733-739, 1991

5. Kosaka K, Kuzuya T, Yoshinaga H, et al: A prospective study of health check examiners for the development of non-insulin-dependent diabetes mellitus. Diabet Med 13:S120-S126, 1996

6. DeFronzo RA, Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 18:173-194, 1991

7. Kosaka K, Kuzuya T, Hagura R, et al: Insulin response to oral glucose load in consistently decreased in established non-insulin-dependent diabetes mellitus. Diabet Med 13:S109-S119, 1996

8. Yoneda H, Ikegami H, Yamamoto Y, et al: Analysis of early-phase insulin responses in non-obese subjects with mild glucose intolerance. Diabetes Care 15:1517-1521, 1992

9. DeFronzo RA, Tobin JA, Andres R, et al: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 237:E214-223, 1979

10. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment. Diabetologia 28:412-419, 1985

11. Matsuda M, DeFronzo R: Insulin sensitivity indices obtained from oral glucose tolerance testing. Diabetes Care 22:1462-1470, 1999

12. Stumvoll M, Mitrakou A, Pimenta W, et al: Use of oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 23:295-301, 2000

13. Gutt M, Davis CL, Spitzer SB, et al: Validation of the insulin sensitivity index comparison with other measures. Diabetes Res Clin Pract 47:177-184, 2000

14. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 22:S5-S19, 1999 (suppl 1)

15. Schwartz MW, Boyko EJ, Kahn SE, et al: Reduced insulin secretion. J Clin Endocrinol Metab 80:1571-1576, 1995

16. Stout RW: Insulin and atheroma. Diabetes Care 13:631-654, 1990

17. Kosaka K, Hagura R, Kuzuya T, et al: Insulin secretory response of diabetics during the period of improvement of glucose tolerance to normal range. Diabetologia 10:775-782, 1974

18. Yoshinaga H, Kosaka K: Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulin-dependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. Diabetes Res Clin Pract 44:129-136, 1999

19. Chen KW, Boyko EJ, Bergstrom RW, et al: Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM. Diabetes Care 18:747-753, 1995

20. Wingard D, Barrett-Connor EL, Ferrara A: Is insulin really a heart disease risk factor? Diabetes Care 18:1299-1304, 1995

21. Del Prato S, Pozzilli P: FIRI: Fasting or false insulin resistance index? Lancet 347:132, 1996