The Role of the Body Mass Index and Triglyceride Levels in Identifying Insulin-Sensitive and Insulin-Resistant Variants in Japanese Non–Insulin-Dependent Diabetic Patients

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Using the minimal model approach shown by Bergman, our group had previously shown 2 variants among non-obese mildly diabetic patients, one with normal insulin sensitivity and the other with insulin resistance. The present study examines whether these 2 variants exist in the ordinary Japanese non–insulin-dependent diabetes mellitus (NIDDM) population and compares the clinical profile between the 2 discrete forms of NIDDM. In addition, we investigated the factors responsible for insulin resistance observed in Japanese NIDDM populations. One hundred eleven untreated Japanese NIDDM subjects (fasting glucose < 10 mmol/L) were assessed for insulin action (homeostasis model assessment [HOMA-IR] = fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5) and the fasting lipid profile. Sixty percent of these patients had normal insulin sensitivity (HOMA-IR < 2.5). The insulin-resistant patients had higher serum cholesterol (188.1 ± 5.2 *v* 182.2 ± 3.9 mg/dL, *P* > .05) and low-density lipoprotein (LDL) cholesterol (501.2 ± 16.7 *v* 469.4 ± 14.8 mg/dL, *P* > .05) than the insulin-sensitive patients, but the difference was not statistically significant. In contrast, the former group had a significantly higher body mass index ([BMI] 26.6 ± 0.8 *v* 21.7 ± 0.4 kg/m², *P* < .0001) and higher serum triglycerides (181.0 ± 16.4 (range, 79 to 545) *v* 95.1 ± 4.1 (range, 36 to 204) mg/dL, *P* < .0001) and lower high-density lipoprotein (HDL) cholesterol (47.2 ± 1.7 *v* 58.2 ± 2.5 mg/dL, *P* < .005) than the latter group. HOMA-IR was related to the BMI. Fifteen of 17 (88%) NIDDM patients with a BMI greater than 27.0 were insulin-resistant, whereas 35 of 38 (92%) NIDDM patients with a BMI less than 21.5 were insulin-sensitive. In the midrange BMI (21.5 to 27.0 kg/m²), patients were equally likely to be insulin-resistant or insulin-sensitive. Analysis of the midrange BMI group showed that HOMA-IR was associated with serum triglycerides (*P* < .0001) but not with the BMI. These data suggest the following conclusions: (1) Japanese NIDDM patients can be classified into 2 populations, one with normal insulin sensitivity and the other with insulin resistance; (2) NIDDM patients with normal insulin action have a low cardiovascular disease risk factor, whereas those with insulin resistance have a markedly increased cardiovascular disease risk factor; and (3) the BMI and serum triglyceride level per se are associated with insulin action in Japanese NIDDM populations.

NON–INSULIN-DEPENDENT diabetes mellitus (NIDDM) is a syndrome characterized by insulin resistance and/or defective insulin secretion.[1] Using the minimal model approach shown by Bergman,[2] we first reported Japanese NIDDM patients without an impairment in insulin action but with a severe derangement in insulin secretion.[3] Our NIDDM patients were unique in that they were mildly diabetic (mean fasting glucose, 6.6 mmol/L; mean glycosylated hemoglobin, 7.5%). Thereafter, Nagasaka et al[4] showed that Japanese NIDDM patients had insulin resistance by the minimal model technique. Interestingly, the Japanese NIDDM patients reported by our team and Nagasaka et al were similar in their fasting glucose and glycosylated hemoglobin levels. These two reports suggest the following hypotheses: (1) Japanese NIDDM patients can be divided into 2 subtypes, one with normal peripheral insulin sensitivity and the other with primary peripheral insulin resistance, and (2) insulin resistance in Japanese NIDDM patients is partly influenced by factors other than the degree of glycemic control.

However, it is not known whether this hypothesis is applicable to only the small group of mildly diabetic patients or to NIDDM patients in general. Hence, the aim of the present study is to investigate if there are 2 subtypes in the general Japanese NIDDM population and, if so, what factor determines insulin resistance in Japanese NIDDM patients. To accomplish this, we recruited 111 Japanese NIDDM outpatients representative of the general NIDDM population and compared the clinical profile between the 2 discrete forms of NIDDM to investigate the factors responsible for the insulin resistance observed in Japanese NIDDM populations.

SUBJECTS AND METHODS

One hundred eleven Japanese NIDDM patients from our clinics were included in the present study. They were treated with diet alone, and NIDDM was diagnosed based on the criteria of the World Health Organization.[5] The duration of diabetes was 10.4 ± 1.4 years (mean ± SE; range, 0.5 to 29.0). Twenty-two normal glucose-tolerant Japanese subjects who previously had minimal model analysis for another purpose (10 men and 12 women aged 22.9 ± 0.7 years; body mass index [BMI], 24.2 ± 1.1 kg/m²) served as controls.[6,7] All subjects ingested at least 150 g carbohydrate for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease or used any medication known to affect lipid metabolism. They did not use antihypertensive medications. Blood was drawn in the morning after a 12-hour fast.

The plasma glucose level was measured in duplicate with an

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Table 1. Characteristics of 111 Japanese NIDDM Patients

Characteristic	Value
Age (yr)	59.7 ± 0.9
BMI (kg/m^2)	22.6 ± 0.5
Fasting glucose (mmol/L)	7.2 ± 0.1
HbA_{1c} (%)	6.8 ± 0.1
Fasting insulin (μU/mL)	8.3 ± 0.7

automatic analyzer (Kyoto-Daiichi-Kagaku, Kyoto, Japan) by the glucose oxidase method. Plasma insulin was analyzed in duplicate using a Phadeseph insulin radioimmunoassay kit (Shionogi, Japan). The coefficient of variation was 4% for insulin greater than 25 μU/mL and 7% for insulin less than 25 μU/mL, respectively.

Cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured by standard enzymatic methods.[8] Low-density lipoprotein (LDL) cholesterol was assayed directly by the method described previously.[9]

The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was calculated with the formula, fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5, as described by Matthews et al.[10] The HOMA-IR value of control subjects was 1.6 ± 0.9 (mean ± SD), and we defined the value greater than 2.5 (mean ± SD of normal control subjects) as an insulin-resistant state and the value less than 2.5 as an insulin-sensitive state. The threshold value for insulin resistance in our study (ie, 2.5) is similar to that (2.77) reported in non-obese subjects with no metabolic disorders reported by Borona et al.[11]

Statistical Analysis

Statistical differences in mean values were determined by the 2-tailed *t* test.[12] Correlations were determined by Pearson linear regression analysis and ANOVA.[12] Data are expressed as the mean ± SE unless otherwise stated.

RESULTS

The characteristics of the 111 subjects (73 men and 38 women) are shown in Table 1. They were all Japanese NIDDM patients with an age range of 40 to 75 years (59.7 ± 0.9) and a BMI of 16.0 to 44.4 kg/m^2 (22.6 ± 0.5). The fasting plasma glucose was 7.2 ± 0.1 mmol/L (range, 4.9 to 9.8) and glycosylated hemoglobin (HbA_{1c}) was 6.8% ± 0.1% (range, 5.0% to 10.6%). Fasting plasma insulin was 8.3 ± 0.7 μU/mL (range, 2.5 to 70.0). The population was grouped according to a HOMA-IR value greater than 2.5 (insulin-resistant type) or less than 2.5 (insulin-sensitive type).

Table 2. Characteristics of Insulin-Resistant and Insulin-Sensitive Japanese NIDDM Patients

Characteristic	Insulin-Resistant	Insulin-Sensitive	*P*
No. of subjects (male/female)	45 (25/20)	66 (44/22)	
HOMA-IR	4.5 ± 0.5	1.5 ± 0.1	<.0001
Age (yr)	60.1 ± 1.1	59.1 ± 1.3	.138
HbA_{1c} (%)	6.9 ± 0.2	6.7 ± 0.2	.147
BMI (kg/m^2)	26.6 ± 0.8	21.7 ± 0.4	<.0001
Triglycerides (mg/dL)	181.0 ± 16.4	95.1 ± 4.1	<.0001
HDL cholesterol (mg/dL)	47.2 ± 1.7	58.2 ± 2.5	.001
Cholesterol (mg/dL)	188.1 ± 5.2	182.2 ± 3.9	.182
LDL cholesterol (mg/dL)	501.2 ± 16.7	469.4 ± 14.8	.103
Fasting glucose (mmol/L)	7.9 ± 0.2	6.8 ± 0.2	<.0001
Fasting insulin (μU/mL)	13.0 ± 1.6	5.2 ± 0.2	<.0001

Table 2 lists the clinical characteristics and clinical profile in the 2 groups of Japanese NIDDM patients. No significant difference was observed for age and HbA_{1c} between the 2 groups. In contrast, patients with insulin resistance had a significantly higher BMI and triglycerides than those with normal insulin sensitivity. HDL cholesterol was significantly lower in NIDDM patients with insulin resistance versus those with normal insulin sensitivity. Serum cholesterol and LDL cholesterol were higher in the insulin-resistant group versus the insulin-sensitive group, but were not statistically significant. Fasting glucose and insulin levels were significantly higher in the insulin-resistant group versus the insulin-sensitive group.

Since there was a positive correlation between the HOMA-IR and the BMI ($r = .650$, $P < .0001$), we next investigated the relationship of insulin sensitivity and insulin resistance to the BMI in these NIDDM patients (Fig 1). Fifteen of 17 (88%) NIDDM patients with a BMI greater than 27.0 were insulin-resistant, whereas 3 of 38 (8%) NIDDM patients with a BMI less than 21.5 were insulin-resistant. In contrast, 27 of 56 (48%) NIDDM patients with a BMI of 21.5 to 27.0 were insulin-resistant.

Table 3 compares the clinical characteristics and clinical

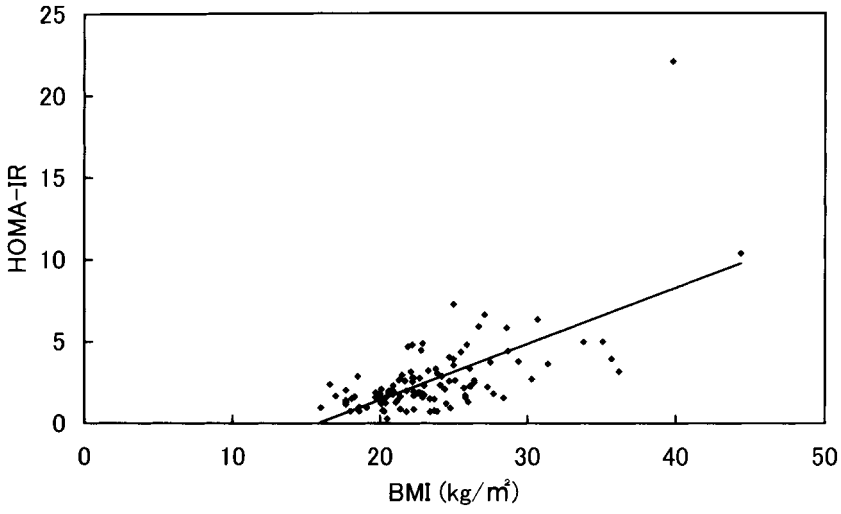

Fig 1. Relationship between the BMI and HOMA-IR in 111 NIDDM patients ($r = .650$, $P < .0001$).

Table 3. Characteristics of Insulin-Resistant and Insulin-Sensitive Japanese NIDDM Patients (21.5 < BMI < 27.0)

Characteristic	Insulin-Resistant	Insulin-Sensitive	*P*
No. of subjects (male/female)	26 (16/10)	28 (18/10)	
HOMA-IR	3.7 ± 0.2	1.6 ± 0.1	<.0001
Age (yr)	61.3 ± 1.8	60.6 ± 1.6	.378
BMI (kg/m^2)	23.8 ± 0.3	23.9 ± 0.3	.486
HbA_{1c} (%)	7.0 ± 0.2	6.8 ± 0.3	.291
Cholesterol (mg/dL)	188.0 ± 5.9	176.5 ± 5.3	.076
LDL cholesterol (mg/dL)	493.6 ± 25.7	472.6 ± 21.0	.264
Triglycerides (mg/dL)	211.7 ± 23.1	96.1 ± 5.2	<.0001
HDL cholesterol (mg/dL)	47.5 ± 2.2	55.5 ± 2.8	.015
Fasting glucose (mmol/L)	7.9 ± 0.2	6.9 ± 0.2	<.0001
Fasting insulin (μU/mL)	10.5 ± 0.7	5.3 ± 0.4	<.0001

profile of insulin-resistant and insulin-sensitive subjects with a BMI of 21.5 to 27.0. There was no significant difference in age, BMI, and HbA_{1c} between the 2 subgroups. Serum cholesterol and LDL cholesterol levels were higher in the insulin-resistant group, but were not statistically significant between the 2 groups. Serum triglycerides, fasting glucose, and insulin were significantly higher in the insulin-resistant group compared with the insulin-sensitive group. Moreover, serum triglycerides were positively correlated with HOMA-IR values in NIDDM patients with a BMI of 21.5 to 27.0 ($r = .774$, $P < .0001$) (Fig 2). In contrast, there was no relationship between HOMA-IR and the BMI in the midrange BMI group ($r = .171$, $P > .05$). HDL cholesterol was significantly lower in the insulin-resistant group compared with the insulin-sensitive group, and an inverse correlation was observed between HDL cholesterol and HOMA-IR values in the midrange BMI group ($r = -.332$, $P < .01$) (Fig 3).

DISCUSSION

Insulin resistance is important not only in the etiology of conditions such as obesity or NIDDM but also in the pathogenesis of cardiovascular disease.[13] Two reliable methods have been widely used to measure insulin resistance in vivo, the euglycemic clamp technique[14] and the minimal model approach.[2,3] However, they are time-consuming and expensive to perform. In contrast, the HOMA-IR as proposed by Matthews et al[10] is technically simple and inexpensive. Matthews et al[10] and Emoto et al[15] reported that the HOMA-IR value is closely correlated with the insulin resistance index assessed by the euglycemic clamp in diabetic patients. Our group[16] and Hermans et al[17] recently demonstrated that the HOMA-IR value is highly correlated with insulin resistance calculated by the minimal model approach in subjects with varying degrees of glucose tolerance. These findings favor the use of HOMA-IR in the assessment of insulin resistance in large population studies. We therefore used HOMA-IR in the present study.

Interestingly, this study disclosed that only 40% of ordinary Japanese NIDDM patients are insulin-resistant. This result is not compatible with the data from DeFronzo[1] and Reaven et al[18] that NIDDM patients are insulin-resistant. The reason for the discrepancy is not known, but it may be due to the racial difference. Haffner et al[19] demonstrated that 92% of NIDDM patients are insulin-resistant in white populations. Banerji et al[20,21] previously disclosed that insulin resistance in black Americans with NIDDM is found in 60% of those with a BMI less than 30 kg/m^2. We previously demonstrated that only 40% of Japanese subjects with impaired glucose tolerance are insulin-resistant.[6]

The present study also shows that NIDDM patients with insulin resistance had significantly higher triglycerides and lower HDL cholesterol than those with normal insulin sensitivity. This dyslipidemia is postulated to be important in the development of accelerated atherosclerosis and coronary heart disease.[13,22] It is thus considered that NIDDM patients with normal insulin action have a low cardiovascular disease risk factor profile, whereas those with insulin resistance have a markedly increased cardiovascular disease risk factor profile, as previously demonstrated in a black NIDDM population.[23] Further study is required to draw a final conclusion that one population has a higher risk for the development of cardiovascular disease but another population does not.

Fasting glucose was higher in the insulin-resistant patients versus the insulin-sensitive group, while HbA_{1c} was not different between groups. The reason for the discrepancy between fasting glucose and HbA_{1c} is not known at present. The daily

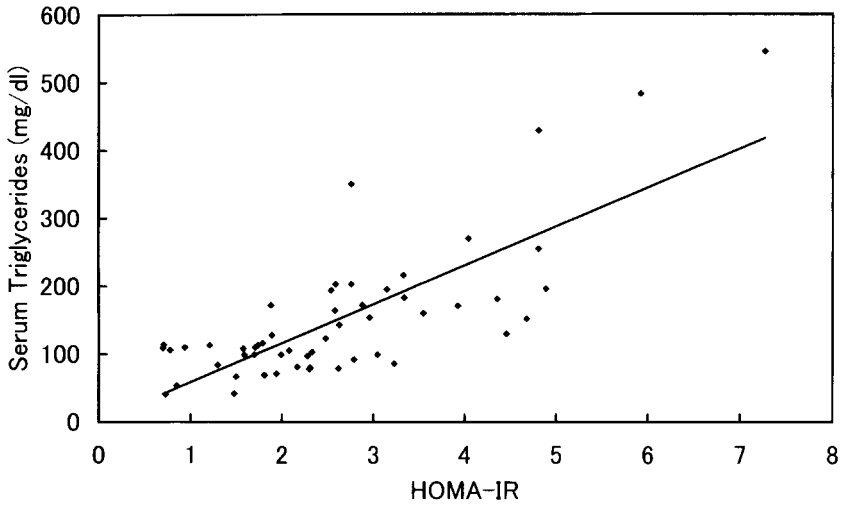

Fig 2. Relationship between HOMA-IR and serum triglycerides in NIDDM patients with a BMI of 21.5-27.0 kg/m^2 ($r = .774$, $P < .0001$).

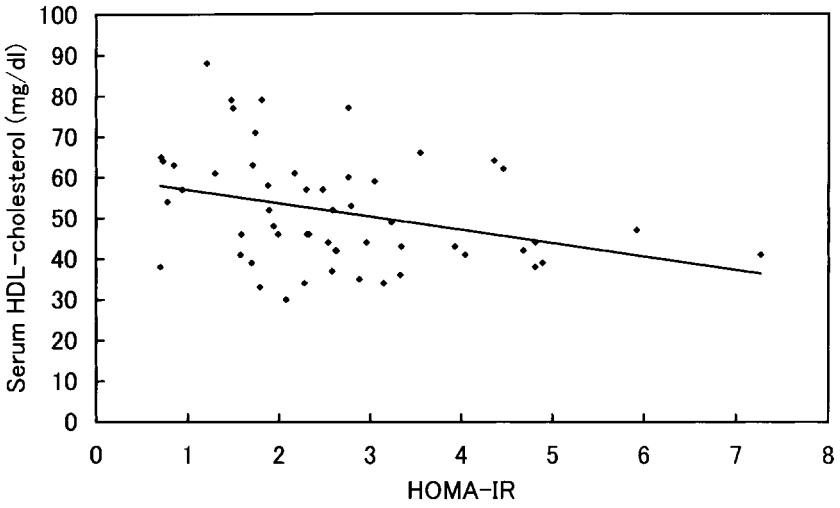

Fig 3. Relationship between HOMA-IR and serum HDL cholesterol in NIDDM patients with a BMI of 21.5-27.0 kg/m² ($r = -.332$, $P < .01$).

glucose profile might affect HbA_{1c} levels, but we did not measure the daily profile.

Of particular interest is that the factors responsible for the evolution of insulin resistance among our Japanese NIDDM patients differ in the range of BMI. Eight percent of NIDDM patients with a BMI less than 21.5 were insulin-resistant, whereas 88% of NIDDM patients with a BMI greater than 27.0 were insulin-resistant, suggesting that the degree of overweight per se determines insulin resistance in Japanese NIDDM patients. However, this did not apply to NIDDM patients with a BMI of 21.5 to 27.0. These patients were equally sensitive or resistant to insulin. Similar results are reported in black NIDDM populations.[24] What factor affects insulin resistance in these patients? The patients with insulin resistance had significantly higher serum triglycerides, although the BMI and cholesterol and HbA_{1c} levels were similar between the 2 populations. In addition, in the midrange BMI group, HOMA-IR values were positively correlated with serum triglyceride levels (Fig 2), but no relation exists between HOMA-IR values and the BMI. It is therefore suggested that hypertriglyceridemia but not the BMI per se is associated with insulin resistance in the midrange BMI group ($21.5 < BMI < 27.0$). This finding suggests that pharmacological agents that decrease serum triglycerides might improve glucose tolerance in NIDDM patients with a BMI of 21.5 to 27.0 by reducing insulin resistance, and the use of triglyceride levels to identify insulin resistance is recommended in Japanese NIDDM patients. In this regard, the previous reports by Jones et al[25] and our team[26] that treatment of NIDDM patients with bezafibrate improves both serum triglycerides and glucose tolerance are very interesting. One might argue that insulin resistance in the midrange BMI group may be a consequence of increased intraabdominal adipose tissue mass,[27] but we did not obtain data on the waist circumference or the waist to hip ratio and did not measure the mass in the present study.

In summary, this study demonstrates that Japanese NIDDM patients can be divided into 2 populations, one with normal insulin sensitivity and the other with insulin resistance, and the latter population has a higher cardiovascular disease risk factor than the former one. Moreover, there is a possibility that the BMI and degree of hypertriglyceridemia per se are independently associated with insulin resistance in Japanese NIDDM populations.

REFERENCES

1. DeFronzo RA: Pathogenesis of type 2 (non–insulin-dependent) diabetes mellitus. Diabetologia 35:389-397, 1992

2. Bergman RN: Toward physiological understanding of glucose tolerance: Minimal-model approach. Diabetes 38:1512-1527, 1989

3. Taniguchi A, Nakai Y, Fukushima M, et al: Pathogenic factors responsible for glucose intolerance in patients with NIDDM. Diabetes 41:1540-1546, 1992

4. Nagasaka S, Tokuyama K, Kusaka I, et al: Endogenous glucose production and glucose effectiveness in type 2 diabetic subjects derived from stable-labeled minimal model approach. Diabetes 48:1054-1060, 1999

5. World Health Organization: Diabetes mellitus: Report of a WHO study group. WHO Tech Rep Ser 727, 1985

6. Taniguchi A, Nakai Y, Doi K, et al: Glucose effectiveness in two subtypes within impaired glucose tolerance: A minimal model analysis. Diabetes 43:1211-1217, 1994

7. Taniguchi A, Nakai Y, Doi K, et al: Insulin sensitivity, insulin secretion, and glucose effectiveness in obese subjects: A minimal model analysis. Metabolism 44:1397-1400, 1995

8. Finley PR, Schifman RB, Williams RJ, et al: Cholesterol in high-density lipoprotein: Use of Mg/dextran sulfate in its enzymatic determination. Clin Chem 18:499-502, 1978

9. Nakamura M, Kishi K, Watazu Y: Evaluation of three total cholesterol methods. Clin Chem 43:S260, 1997 (suppl)

10. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: Insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412-419, 1985

11. Borona E, Kiechl S, Willeit J, et al: Prevalence of insulin resistance in metabolic disorders. The Bruneck Study. Diabetes 47:1643-1649, 1998

12. Snedecor GW, Cochran WG: Statistical Methods. Ames, IA, Iowa State University Press, 1967, pp 59-65

13. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1998

14. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: A method for quantifying insulin secretion and insulin resistance. Am J Physiol 237:E214-E223, 1979

15. Emoto M, Nishizawa Y, Maekawa K, et al: Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes Care 22:818-822, 1999

16. Fukushima M, Taniguchi A, Sakai M, et al: Homeostasis model assessment as a clinical index of insulin resistance: Comparison with the minimal model analysis. Diabetes Care 22:1911-1912, 1999 (letter)

17. Hermans MP, Levy JC, Morris RJ, et al: Comparison of insulin sensitivity tests across a range of glucose tolerance from normal to diabetes. Diabetologia 42:678-687, 1999

18. Reaven GM, Hollenbeck CB, Chen YDI: Relationship between glucose tolerance, insulin secretion, and insulin action in non-obese individuals with varying degrees of glucose tolerance. Diabetologia 32:52-55, 1989

19. Haffner SM, D'Agostino R Jr, Mykkanen L, et al: Insulin sensitivity in subjects with type 2 diabetes. Relationship to cardiovascular risk factors: The Insulin Resistance Atherosclerosis Study. Diabetes Care 22:562-568, 1999

20. Banerji MA, Lebovitz HE: Insulin-sensitive and insulin-resistant variants in NIDDM. Diabetes 38:784-792, 1989

21. Chaiken R, Banerji MA, Huey H, et al: Do blacks with NIDDM have an insulin-resistance syndrome? Diabetes 42:444-449, 1993

22. Miller GJ, Miller NE, Ashcroft MT: Inverse relationship in Jamaica between plasma high density lipoprotein cholesterol concentration and coronary-disease risk as predicted by multiple risk factors. Clin Sci Mol Med 51:475-482, 1976

23. Banerji MA, Lebovitz HE: Coronary heart disease risk factor profiles in black patients with non–insulin-dependent diabetes mellitus: Paradoxic patterns. Am J Med 91:51-58, 1991

24. Banerji MA, Lebovitz HE: Insulin action in black Americans with NIDDM. Diabetes Care 15:1295-1302, 1992

25. Jones IR, Swai A, Taylor R, et al: Lowering of plasma glucose concentrations with bezafibrate in patients with moderately controlled NIDDM. Diabetes Care 13:855-863, 1990

26. Fukushima M, Taniguchi A, Sakai M, et al: Effects of bezafibrate on insulin sensitivity in non-obese Japanese NIDDM patients. Diabetes Care 23:259, 2000 (letter)

27. Banerji MA, Chaiken RL, Gordon D, et al: Does intra-abdominal adipose tissue in black men determine whether NIDDM is insulin-resistant or insulin-sensitive? Diabetes 44:141-146, 1995