Diabetes, Exercise, and Atherosclerosis

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Regular exercise may diminish the risk for atherosclerotic vascular disease in patients with non-insulin-dependent (type II) diabetes and in the general population. The basis for this effect of exercise may be its ability to diminish or prevent hyperinsulinemia, insulin resistance, and/or increases in intra-abdominal adipose mass. These abnormalities are associated with premature atherosclerotic vascular disease, essential hypertension, type II diabetes, and certain dyslipoproteinemias, and most likely precede them. They also have been implicated in the pathogenesis of these disorders. We propose that the high prevalence of hyperinsulinemia and insulin resistance in individuals leading a western life-style accounts for the reported benefit of physical activity in preventing coronary heart disease in the general population. We also propose that exercise (and diet) are most likely to be effective when initiated in young individuals, before the onset of irreversible vascular alterations, and when life-style changes may be more acceptable. Early identification of such individuals may be possible on the basis of family history, the presence of components of the hyperinsulinemia-insulin resistance syndrome, and/or central obesity. One such group that may already have been identified is women with gestational diabetes.

Macrovascular disease caused by atherosclerosis is the major cause of mortality in patients with non-insulin-dependent (type II) diabetes. Coronary heart disease, stroke, and peripheral vascular disease are all more common in diabetes and occur at an earlier age (1). Typical findings are those of the Framingham study in which a 2- to 6-fold greater prevalence of these disorders was found in diabetic men and women (aged 45–74) than in the general population (2). This increased prevalence of atherosclerotic vascular disease appears to be caused, at least in part, by environmental factors (1). Native Japanese with diabetes living in Hawaii have more than twice the rate of ischemic heart disease as Japanese of comparable age with diabetes living in Japan (3). In contrast, the prevalence of retinopathy in the two groups was identical. The basis for the different rates of ischemic heart disease was not ascertained; however, the Japanese living in Hawaii were more obese, and they had more hypertension and higher levels of total plasma cholesterol and triglycerides than their counterparts in Japan. Similar increases in coronary heart disease and/or its risk factors and an increased incidence of type II diabetes itself have been reported in other populations that have adapted a western life-style (4–8). The identity of the environmental factor(s) responsible for this has yet to be established with certainty. Obvious candidates include diet, stress, and diminished physical activity.

EXERCISE AND ATHEROSCLEROSIS — As reviewed elsewhere in Schneider et al. (9) and Ruderman et al. (10), epidemiological studies suggest that regular exercise (11) and physical fitness (12) were associated with decreased coronary heart disease in the general population. Studies in primates fed an atherogenic diet for 18 mo showed that exercise, independent of its effect on plasma lipids, markedly diminished the severity of atherosclerosis (13). Studies in humans indicated that regular exercise can diminish risk factors for coronary heart disease, such as hypertension (14,15), diminished high-density lipoprotein (HDL) cholesterol, and hypertriglyceridemia (9). Although much of the experimental evidence has been obtained in nondiabetic subjects, there is little reason to believe that the findings do not apply to patients with type II diabetes. Indeed, it is one of our fundamental premises that much of the reported benefit of exercise in the general

Table 1—*Prevalence of ischemic heart disease and retinopathy in diabetics in Japan, Hawaii, and England*

	ISCHEMIC HEART DISEASE* (%)	RETINOPATHY† (%)
JAPANESE		
HIROSHIMA	14	57
HAWAII	33	50
CAUCASIAN		
HAWAII	33	
ENGLAND		55

From Kawate et al. (3).
* Postmortem studies in patients at least 40 yr old.
† Diabetic patients of 10- to 19-yr duration.

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Table 2—*Characteristics of athletic and sedentary middle-aged Swedish men*

	SKIERS	NONATHLETES
AGE (YR)	54	55
WEIGHT (KG)	71	75
BODY FAT (KG)	10*	16
TRIGLYCERIDES (MG/DL)	80*	109
CHOLESTEROL (MG/DL)	203*	257
GLUCOSE (MG/DL)		
FASTING	73	64
POSTGLUCOSE (1 H)	79*	108
INSULIN (μU/ML)		
FASTING	2*	10
POSTGLUCOSE (1 H)	34*	95

From Bjorntorp et al. (27). See text for details.
* Significantly different from nonathletes, $P < 0.05$.

population could be caused by its effect on the large number of people at risk for type II diabetes and associated disorders, such as hypertension and hypertriglyceridemia.

A possible basis for the antiatherogenic effects of exercise is its ability to diminish plasma insulin levels and enhance insulin sensitivity. Hyperinsulinemia and insulin resistance are more prevalent in individuals with atherosclerotic vascular disease than in the general population, even in the absence of impaired glucose tolerance or overt obesity (1,16). The reason for this is unclear; however, hyperinsulinemia and insulin resistance have been implicated in the pathogenesis of such coronary disease risk factors as essential hypertension (14,17–19), hypertriglyceridemia (20), and impaired fibrinolytic activity (21). In addition, they may be independent risk factors for coronary heart disease (22–24). In patients with type II diabetes, higher insulin and/or C-peptide levels have been observed in individuals with atherosclerotic vascular disease, both at the time of diagnosis (25) and later (26). Furthermore, they occur in patients treated with diet, oral agents, and insulin (26) and, as will be discussed later, they most likely antedate the vascular disease.

That regular exercise diminishes plasma insulin levels and enhances insulin action in humans was first suggested by studies in trained athletes. In an oft-quoted study, Bjorntorp and coworkers (27) compared two groups of normal-weight, middle-aged Swedish businessmen: one group consisted of individuals who were highly trained cross-country skiers and the other group consisted of age- and weight-matched nonathletes (Table 2). Neither group was diabetic; however, the athletes had lower insulin levels and a much smaller increase in blood glucose during a glucose tolerance test. Plasma triglycerides and total cholesterol were also lower in the athletes as was total body fat. Similar differences in insulin sensitivity and plasma lipids, and an increase in HDL cholesterol in athletes have been reported by others (9). Improvement in insulin sensitivity has been reported in sedentary individuals who begin to exercise regularly after several weeks (28,37). The mechanism for the increase in insulin sensitivity induced by regular exercise is not known. It has been demonstrated in muscle of acutely and chronically exercised rats (29,30) and humans (10,37). In chronically exercised rats, it appears to be associated with an increase in the number of both insulin receptors (31) and the insulin-sensitive glucose transport protein (GLUT4) (32) found in muscle. Whether regular exercise alters insulin action in tissues more directly involved in atherosclerosis and hypertension (e.g., blood vessels and kidneys) remains to be determined.

EXERCISE AND TYPE II DIABETES

— Because type II diabetic patients are often insulin-resistant and hypertriglyceridemic, a number of groups have examined the effects of regular exercise on glycemic control and risk factors for atherosclerotic vascular disease in these patients (9,10). A particularly revealing study is that of Schneider et al. (33), in which a decrease in HbA_{1c} of 12% was observed in a group of middle-aged type II diabetics who underwent a hospital-based exercise program for 6 wk. An important finding was that improvement in HbA_{1c} was related to the cumulative effect of the individual exercise bouts, rather than improved fitness per se. Thus, glucose tolerance was improved 12 and 17 h, but not 3 days, after the last bout of exercise in these patients. Quantitatively similar conclusions have been drawn from studies in nondiabetic athletes during detraining (34,35). It has also been shown that physical training can lower plasma triglycerides, increase insulin sensitivity (9,36,37), and possibly increase fibrinolytic activity (38) in patients with type II diabetes. In general, the greatest improvement in glycemic control occurs in patients with mild diabetes (FPS < 200 mg/dl) (33,36,39, 40). As shown by Holloszy et al. (40,41), such individuals are more hyperinsulinemic than diabetic patients with more severe hyperglycemia, and their insulin levels, like their blood glucose levels, decrease with training. (There have also been reports of individuals with type II diabetes in whom improved glycemic control is associated with increased insu-

Table 3—*Changes in blood pressure in women with low and high plasma insulin levels after 6 mo of physical training*

	LOW INSULIN	HIGH INSULIN
AGE (YR)	39	36
WEIGHT (KG)	77	81
INITIAL BLOOD PRESSURE (MMHG)	130/86	129/85
INITIAL INSULIN (μU/ML)	8	16*
ΔINSULIN	+3	−7*
ΔBLOOD PRESSURE		
SYSTOLIC	−3	−6*
DIASTOLIC	−3	−10*

From Krotkiewski et al. (14). The hyperinsulinemic group also initially had moderately higher plasma triglyceride levels that decreased during training. Loss of adipose mass after 6 mo was the same in the two groups.
* Significantly different from low insulin group, $P < 0.05$.

lin secretion [39,42]. Possibly diminished blood glucose levels secondary to exercise diminishes glucose toxicity in the islets [43,44] of such patients.) In one such group, intense training for 1 yr normalized glucose tolerance, substantially decreased plasma triglycerides and cholesterol, and increased HDL cholesterol levels (41). A moderate loss of adipose tissue mass in these individuals somewhat confounds the role of exercise in producing these changes; nevertheless, the results are very impressive. That the training required to cause changes in patients with type II diabetes need not be prolonged was recently underscored by the demonstration of Rogers et al. (40), that an exercise program can improve glucose tolerance in such patients in as little as 1 wk.

Significant changes in blood pressure were not reported in any of the published studies in diabetic patients; however, predominantly normotensive patients were evaluated (33,36). It is now recognized that essential hypertension is associated with insulin resistance and hyperinsulinism even in the absence of diabetes and overt obesity (18,19). Furthermore, physical training has been shown to cause modest decreases in systolic and diastolic blood pressures (Table 3) in patients with mild hypertension (14,15). The greatest decrease in blood pressure appears to occur in individuals in whom exercise diminishes hyperinsulinemia (14).

THE METABOLICALLY OBESE NORMAL-WEIGHT (MONW) INDIVIDUAL, SYNDROME X, AND CENTRAL OBESITY—

Although the evidence that regular exercise can improve glucose tolerance, diminish insulin resistance, and improve coronary risk factors in some patients with type II diabetes is reasonably compelling, the therapeutic efficacy of exercise in such patients may be questioned. In most of them, the diagnosis of type II diabetes or impaired glucose tolerance is made when they are >40 yr of age and likely to be resistant to embarking on a lifelong exercise (or diet) program (45). Furthermore, many of them already have clinically significant coronary heart disease (46,47). These factors do not negate the therapeutic value of exercise; however, they strongly suggest that exercise and other preventive measures (e.g., diet) may be more efficacious if they are instituted earlier in life and before the onset of overt diabetes (i.e., in patients at risk for developing the diabetic syndrome).

Among the questions raised by this suggestion is, "How are such patients to be identified?" We believe that the answer is, at least in part, by the presence of hyperinsulinemia and central adiposity.

Hyperinsulinemia and insulin resistance invariably accompany adult-onset obesity and are thought to provide a link between it and type II diabetes, hypertension, certain dyslipoproteinemias, and atherosclerosis (16,17,48). In addition, hyperinsulinemia and insulin resistance often appear to be present in people with these disorders who are not overtly obese (49,50). Such MONW individuals may be relatively common in the general population. In a study of Italian factory workers reported by Zavaroni et al. (51), 240 nonobese (mean body mass index 24.7 kg/m^2) men (mean age 39 yr) were divided into two subgroups on the basis of their insulin response during an oral glucose tolerance test. Individuals with plasma insulin levels >2SD greater than the mean of the entire group were classified as hyperinsulinemic (52). As shown in Table 4, the two groups were identical in age, body mass index, and fasting plasma glucose levels. However, the hyperinsulinemic subjects had significantly higher systolic and diastolic blood pressures, higher plasma concentrations of triglycerides and glucose (1 h postglucose load), and a lower plasma level of HDL cholesterol. They had many of the risk factors for coronary heart disease often seen in individuals with obesity, impaired glucose tolerance, and overt type II diabetes. Reaven (20) has suggested the term syndrome X to describe the frequent concurrence of these risk factors in the same individual. Recent studies suggest that hyperinsulinemia and insulin resistance, as found in syndrome X and MONW individuals, are early events that precede the onset of

Table 4—*Characteristics of Italian factory workers with hyperinsulinemia and normal glucose tolerance*

	Hyperinsulinemia	Normal insulin
Age (yr)	39	39
Body mass index	24.7	24.7
Glucose (mg/dl)		
Fasting	86	86
Postglucose (1 h)	110*	94
Insulin (pmol/ml)		
Fasting	0.14*	0.07
Postglucose (1 h)	0.94*	0.35
Triglycerides (mM)	1.7*	1.2
Cholesterol (mM)	5.1	4.8
HDL cholesterol (mM)	1.2*	1.4
Blood pressure (mmHg)		
Systolic	126*	119
Diastolic	85*	78

From Zavaroni et al. (51). Measures of central obesity were not reported in this study. HDL, high-density lipoprotein.
* Significantly different from normal insulin group, $P < 0.05$.

Table 5—*Baseline characteristics of Japanese-American men who did and did not develop type II diabetes in 2.5 yr*

	Diabetes (15)	No diabetes (131)
Initial age (yr)	64	61
Fasting glucose (mg/dl)	110*	100
Fasting C-peptide (nM)	1.2*	0.9
Body mass index (kg/m^2)	26	25
Intra-abdominal fat (cross-section area: cm^2)†	150*	109

From Bergstrom et al. (58).
* Significantly different from diabetic group, $P < 0.05$.
† Measured by CAT Scan.

clinically significant vascular disease and diabetes. Thus, they have been observed both in relatives of diabetic patients (52) and in Pima Indians (6), who later develop type II diabetes. In the Bogalusa study (53), hyperinsulinemia has been found in association with modest elevations of blood pressure, alterations in plasma triglycerides, and total and HDL cholesterol in school-aged children (53).

A number of reports suggest that these hyperinsulinemic syndromes may be associated with a site-specific increase in intraabdominal fat, independent of the size of other adipose tissue depots (54–56). Individuals with this central or android pattern of obesity are insulin resistant and are at increased risk for diabetes (57,58). In type II diabetics, this pattern of obesity is associated with an increased prevalence of hypertension and coronary heart disease (59). The cause of hyperinsulinemia and insulin resistance in these patients is unknown. It may relate to the fact that adipocytes in intraabdominal fat are more lipolytic and less sensitive to the antilipolytic effect of insulin than adipocytes from subcutaneous abdominal fat (60). An increased release of free fatty acids from an enlarged intraabdominal fat deposit hypothetically could cause insulin resistance by inhibiting hepatic insulin degradation, enhancing hepatic glucose production, or depressing insulin action in the periphery (55).

A study that illustrates the potential predictive value of central obesity measurements is that of Bergstrom et al. (58), who examined the baseline characteristics of middle-aged Japanese-American men who later developed or did not develop diabetes. As shown in Table 5, the incidence of diabetes is extremely high in this population: >10% of the ostensibly normal men who entered the study became diabetic over 2.5 yr. Those who became diabetic had significantly greater fasting plasma glucose and C-peptide levels and a larger intraabdominal fat depot, as measured by CAT scan, at the time they entered the study. They could not be distinguished from individuals who remained nondiabetic on the basis of body mass index or routinely used measures of site-specific adipose tissue distribution, such as the subscapular/triceps skinfold thickness ratio. The potential importance of central obesity as a predictor of syndrome X and the MONW state is further suggested by the results of the Bogalusa study in which school children (9–14 yr of age) were studied for cardiovascular risk factors, and the results related to adiposity. As noted previously, correlations were found between plasma insulin levels and systolic and diastolic blood pressure elevation, increased plasma triglycerides

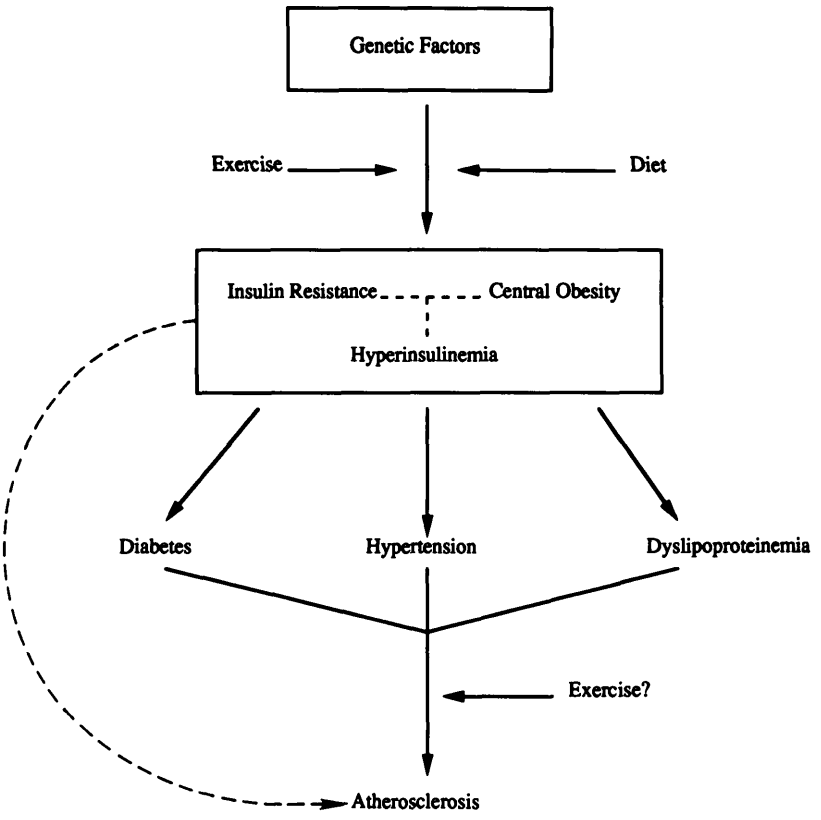

Figure 1—*Exercise and atherosclerosis. According to this scheme, exercise (and diet) can modify the effect of genetic factors that predispose an individual to hyperinsulinemia, insulin resistance, and central obesity. This, in turn, will diminish the propensity of such individuals to develop type II diabetes, hypertension, and certain dyslipoproteinemias. The antiatherogenic action of exercise could be attributable to all of these effects. The report that exercise diminishes the severity of coronary heart disease in monkeys fed an atherogenic diet (13), independent of changes in plasma lipids, glucose, or blood pressure, suggests that it also has an antiatherogenic effect at some later step in the atherosclerotic process.*

Table 6—***Plasma insulin levels in 12-yr-old school children according to degree of central obesity (Bogalusa study)***

	DEGREE OF CENTRAL OBESITY		
PERIPHERAL FAT	LOW	MIDDLE [INSULIN (μU/ML)]	HIGH
LOW	52	74	91
HIGH	38	62	87

From Freedman et al. (61). Estimates of central and peripheral fat were based on skinfold measurements. Insulin levels were determined 1 h after the administration of an oral glucose load.

Table 7—*Identifying characteristics of young insulin-resistant hyperinsulinemic individuals in whom exercise (and diet) hypothetically would diminish risk for atherosclerotic vascular disease*

1. IMPAIRED GLUCOSE TOLERANCE
2. INCREASED VERY-LOW-DENSITY LIPOPROTEIN TRIGLYCERIDE
3. DECREASED HIGH-DENSITY LIPOPROTEIN CHOLESTEROL
4. ESSENTIAL HYPERTENSION
5. CENTRAL OBESITY
6. GESTATIONAL DIABETES
7. FAMILY HISTORY 1, 2, 3, AND 4
8. FAMILY HISTORY OF PREMATURE CORONARY HEART DISEASE*

* Upward of 50% of white men <55 yr of age who enter a hospital for a myocardial infarction may have impaired glucose tolerance, previously undiagnosed diabetes, and/or hypertriglyceridemia (63).

and cholesterol, and decreased HDL cholesterol levels in these children (53). In addition, a clear-cut relationship was observed between the presence of central obesity and hyperinsulinemia, independent of peripheral fat (61) (Table 6).

CONCLUSIONS— We reviewed evidence suggesting that regular exercise diminishes the risk for atherosclerotic vascular disease in patients with type II diabetes and in the general population. The basis for such an effect may be the ability of exercise to diminish plasma insulin levels and insulin resistance. Although a causal relationship has not been established (62), hyperinsulinemia and insulin resistance are clearly associated with premature atherosclerotic vascular disease, essential hypertension, type II diabetes, and certain dyslipoproteinemias, and most likely precede them. Central obesity is also present in many individuals who later develop these disorders; however, its relationship to hyperinsulinemia and insulin resistance remains to be established. Based on these findings, we propose the following:

1. The role of exercise in preventing coronary heart disease is principally caused by its effects on hyperinsulinemia, insulin resistance, and/or intra-abdominal adipose mass (Fig. 1).

2. The high prevalence of these abnormalities in individuals leading a western life-style accounts for the reported benefits of physical activity in epidemiological studies.

3. Exercise and diet are most likely to be effective in preventing coronary heart disease when they are initiated in young individuals (i.e., before the onset of irreversible vascular alterations and when life-style changes may be more acceptable).

4. Early identification of such individuals may be possible on the basis of family history, the presence of components of the hyperinsulinemia-insulin resistance syndrome, and/or central obesity (Table 7). Once group that may already be routinely identified is women with gestational diabetes.

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References

1. Ruderman NB, Haudenschild C: Diabetes as an atherogenic factor? *Prog Cardiovasc Dis* 26:373–412, 1984
2. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. *JAMA* 241:2035–38, 1979
3. Kawate R, Yamkido M, Nishimoto Y: Diabetes mellitus and its vascular complications in Japanese migrants on the island of Hawaii. *Diabetes Care* 2:161–70, 1979
4. Fujimoto WY, Leonetti DL, Kinyoon JC, Shuman WP, Stolov WP, Wahl RW: Prevalence of complications among second generation Japanese American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. *Diabetes* 36:730–39, 1987
5. O'Dea K: Marked improvement in carbohydrate and lipid metabolism in diabetic Australian aborigines after temporary reversion to traditional lifestyle. *Diabetes* 33:596–603, 1984
6. Lillioja S, Bogardus C: Obesity and insulin resistance: lessons learned from the Pima Indians. *Diab Metab Rev* 4:517–40, 1988
7. Stern MR, Rosenthal M, Haffner SM, Hazuda HP, Franco LJ: Sex differences in the effects of sociocultural status on diabetes and cardiovascular risk factors in Mexican-Americans: The San Antonio Heart Study. *Am J Epidemiol* 120:834–51, 1984
8. Zimmet PZ: Primary prevention of diabetes mellitus. *Diabetes Care* 11:258–62, 1988
9. Schneider SH, Vitug A, Ruderman N: Atherosclerosis and physical activity. *Diab Metab Rev* 1:513–53, 1986
10. Ruderman NB, Apelian AZ, Schneider SH: Exercise in therapy and prevention of type II diabetes. *Diabetes Care* 13 (Suppl. 4):1163–68, 1990
11. Paffenbarger RS, Wing AL, Hyde RT: Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 108:161–75, 1978
12. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS: Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men: the Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med* 319:1379–1384, 1988
13. Kramsch DM, Aspen AJ, Abramowitz BM, Kriemendahl T, Hood WB Jr: Reduction of coronary atherosclerosis by moderate conditioning exercise in monkeys on an atherogenic diet. *N Engl J Med* 305:1483–89, 1981
14. Krotkiewski M, Mandrovkas K, Sjostrom L, Sullivan L, Wetterquist H, Bjorntrop P: Effects of long-term physical training on body fat, metabolism, and blood pressure in obesity. *Metabolism* 28:650–58, 1979
15. Nelson L, Jennings GL, Ester MD, Korner PI: Effect of changing levels of physical activity on blood pressure and hemodynamics in essential hypertension. *Lancet* 2:474–76, 1986

16. Stout RW: Overview of the association between insulin and atherosclerosis. *Metabolism* 34 (Suppl. 1):7–12, 1985
17. Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, Shitrit A, Fuchs Z: Hyperinsulinemia: a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 75:809–17, 1985
18. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli B, Brandi L, Bevilacqua S: Insulin resistance in essential hypertension. *N Engl J Med* 317:350–57, 1987
19. Reaven G, Hoffman B: A role for insulin in the etiology and course of hypertension. *Lancet* 2:435–36, 1987
20. Reaven GM: Banting Lecture, 1988. Role of insulin resistance in human diabetes. *Diabetes* 37:1595–1607, 1988
21. Juhan-Vague I, Roul C, Alessi MC, Ardissone JP, Heion H, Vague P: Increased plasminogen activator inhibitor in non-insulin-dependent diabetic patients: relationship with plasma insulin. *Thromb Haemostasis* 61:370–73, 1989
22. Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular disease mortality with reference to glucose and insulin concentrations. *Diabetes Care* 2:154–60, 1979
23. Ducimetiere P, Eschwege E, Papoz L, Richard JL, Claude JR, Rosselin G: Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease in a middle-aged population. *Diabetologia* 19:205–10, 1980
24. Pyorala K, Savolainen E, Kavkola J, Haapakoski H: Plasma insulin as a coronary heart disease risk factor: relationship to other risk factors and predictive value during 9½ year follow-up of the Helsinki Policeman study population. *Acta Med Scand* 701 (Suppl.):38–52, 1985
25. Uusitupa MIJ, Nishkanene LK, Siitonen O, Voutilainen E, Pyorala MD: Five year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin levels and abnormalities in lipoprotein composition in non-insulin dependent diabetic and non-diabetic subjects. *Circulation* 82:27–36, 1980
26. Standl E, Janka HV: High serum insulin concentrations in relation to other cardiovascular risk factors in macrovascular disease of type II diabetes. *Horm Metab Res* 15 (Suppl. 1):46–51, 1985
27. Bjorntorp P, Fahlen M, Grimby G: Carbohydrate and lipid metabolism in middle-aged physically well-trained men. *Metabolism* 21:1037–44, 1972
28. Bjorntorp P, De Jounge K, Sjostrom L, Sullivan L: The effect of physical training on insulin production in obesity. *Metabolism* 19:631–38, 1976
29. Richter EA, Garetto LP, Goodman MN, Ruderman NB: Muscle glucose metabolism following exercise in the rat. *J Clin Invest* 69:785–93, 1982
30. Mondon CR, Dolkas CB, Reaven GM: Site of enhanced insulin sensitivity in exercise-trained rats. *Am J Physiol* 239: E169–77, 1980
31. Dohm GL, Sinha MK, Caro JF: Insulin receptor binding and protein kinase activity in muscles of trained rats. *Am J Physiol* 252:E170–75, 1987
32. Rodnick KJ, Holloszy JO, Mondon CE, James DE: Effects of exercise training on insulin-regulatable glucose transporter protein levels in rat skeletal muscle. *Diabetes* 39:1425–29, 1990
33. Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB: Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin dependent) diabetes. *Diabetologia* 26:353–60, 1984
34. Burstein R, Polychronakos C, Toews CJ, MacDougall JD, Guyda HJ, Posner BI: Acute reversal of enhanced insulin action in trained athletes. *Diabetes* 34:750–60, 1985
35. Heath GW, Gavin JR, Hinderliter JM, Hagberg JM, Bloomfield SA, Holloszy J O : Effects of exercise and lack of exercise on glucose tolerance and insulin sensitivity. *J Appl Physiol* 55:512–17, 1983
36. Trovati M, Carta Q, Cavlot F, Vitali S, Banaudi C, Lucchina PG, Fiocchi F, Emanuelli G, Lenti G: Influence of physical training on blood glucose control, glucose tolerance, insulin secretion and insulin action in non-insulin dependent diabetes. *Diabetes Care* 7:416–20, 1984
37. Koivisto VA, Yki-Jarvinen H, DeFronzo RA: Physical training and insulin sensitivity. *Diab Metab Rev* 1:445–81, 1986
38. Schneider SH, Kim HC, Khachadurian AK, Ruderman NB: Impaired fibrinolytic response to exercise in type II diabetes: effects of exercise and physical training. *Metabolism* 37:924–29, 1988
39. Ronnemaa T, Mattila K, Lehtonen A, Kallio V: Factors related to improved metabolic control in type 2 (non-insulin dependent) diabetic patients during long-term physical exercise: a controlled randomized study (Abstract). *Diabetologia* 27:326A, 1984
40. Rogers MA, Yamamoto C, King DS, Hagberg JM, Ehsani AA, Holloszy JO: Improvement in glucose tolerance after 1 week of exercise in patients with mild NIDDM. *Diabetes Care* 11:613–18, 1988
41. Holloszy JO, Schultz J, Kusnierkiewicz J, Hagberg JM, Ehsani AA: Effects of exercise on glucose tolerance and insulin resistance. *Acta Med Scand Suppl* 711:55–65, 1986
42. Krotkiewski M, Loaroth P, Manrwoukas K, Wroblewksi Z, Rebuffe-Serive M, Holme G, Smith U, Bjorntorp P: Effects of physical training on insulin secretion and effectiveness and glucose metabolism in obesity and type 2 diabetes (non-insulin dependent) diabetes mellitus. *Diabetologia* 28:881–90, 1985
43. De Fronzo RA: Lilly Lecture, 1987. The triumvirate β-cell, muscle and liver: a collusion responsible for NIDDM. *Diabetes* 37:667–87, 1988
44. Unger RH, Grundy S: Hyperglycemia as an inducer as well as a consequence of impaired islet function and insulin resistance. *Diabetologia* 28:119–21, 1985
45. Skarfors ET, Wegener TA, Lithell H, Selinus I: Physical training as treatment for type 2 (non-insulin dependent) diabetes in elderly men. A feasibility study over 2 years. *Diabetologia* 30:930–33, 1987
46. Nesto RW, Phillips RT, Kett KG, Hill T, Perper E, Young E, Leland S: Angina and exertional myocardial ischemia in diabetic and non-diabetic patients: assessment by exercise thallium scintigraphy. *Ann Intern Med* 108:170–75, 1988
47. Uusitupa M, Siltonen O, Pyorala K, Aro A, Hersio K, Pentilla I, Voutilainen E: The relationship of cardiovascular risk factors to the prevalence of coronary

heart disease in recently diagnosed type II (non-insulin-dependent) diabetes. *Diabetologia* 28:653–59, 1985
48. Christlieb AK, Krolewski AS, Warram JH, Soeldner JS: Is insulin the link between obesity and hypertension? *Hypertension* 7 (Suppl. 2):54–57, 1985
49. Ruderman NB, Schneider SH, Berchtold P: The metabolically-obese, normal-weight individual. *Am J Clin Nutr* 34: 1617–21, 1981
50. Ruderman NB, Berchtold P, Schneider SH: Obesity-associated disorders in normal weight individuals. *Int J Obesity* 6:151–57, 1982
51. Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passeri M, Reaven G: Risk factors for coronary artery disease in healthy persons with hyperinsulinmia and normal glucose tolerance. *N Engl J Med* 320:702–706, 1989
52. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in offspring with diabetic parents. *Ann Intern Med* 190:909–15, 1990
53. Burke GL, Webber LS, Srinivasan SR, Radhakrishnamurthy B, Freeman DS, Berenson GS: Fasting plasma glucose and insulin levels and their relationship to cardiovascular risk factors in children: Bogalusa heart study. *Metabolism* 35: 441–46, 1986
54. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW: Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 54:254–60, 1982
55. Bjorntorp P: Abdominal obesity and the development of non-insulin dependent diabetes mellitus. *Diabetes Metab Rev* 4:615–27, 1988
56. Stern MP, Haffner SM: Body fat distribution and hyperinsulinemia as risk factor, for diabetes and cardiovascular disease. *Arteriosclerosis* 6:123–30, 1986
57. Ohlson LO, Larsson B, Suardsud K, Welin L, Eriksson H, Wilhelmsen R, Bjorntorp P, Tibblin G: The influence of body fat distribution on the incidence of diabetes mellitus 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 34:1055–58, 1988
58. Bergstrom RW, Newell-Morris LL, Leonetti DL, Shuman WP, Wahl PW, Fujimoto WY: Association of elevated fasting C-peptide level and increased intra-abdominal fat distribution with development of NIDDM in Japanese-American men. *Diabetes* 39:104–11, 1990
59. Van Gaal L, Rillaerts E, Greten W, De Leeuw I: Relationship of body fat distribution to atherogenic risk in NIDDM. *Diabetes Care* 11:103–106, 1988
60. Bolinfrt J, Kager L, Ostman J, Arner P: Differences in the receptor and post-receptor levels between human omental and subcutaneous adipose tissue in the action of insulin lipolysis. *Diabetes* 32: 117–23, 1983
61. Freedman DS, Srinivasan SR, Burke GL, Shear CL, Smoak CG, Harsha DW, Webber LS, Berenson GS: *Am J Clin Nutr* 46:403–10, 1987
62. Genuth S: Insulin use in NIDDM. *Diabetes Care* 13:1240–64, 1990
63. Wahlquist, Carlson LA: Serum lipids, glucose tolerance and their interrelation studied in ischemic cardiovascular disease. *Acta Med Scand* 180:307–14, 1966