Antihypertensive Therapy With Enalapril Improves Glucose Storage and Insulin Sensitivity in Hypertensive Patients With Non–Insulin-Dependent Diabetes Mellitus

H. Vuorinen-Markkola and H. Yki-Järvinen

A double-blind, placebo-controlled, 4-week trial was performed to determine the antihypertensive and metabolic effects of enalapril (20 to 40 mg/d) in 16 hypertensive patients with non–insulin-dependent diabetes mellitus (NIDDM) aged 55 ± 2 years and with a body mass index of 29 ± 1 kg/m^2. Glucose utilization was determined after an overnight fast and during insulin stimulation at 0 and 4 weeks (methods: euglycemic clamp, [3-^{3}H]glucose infusion, indirect calorimetry). Enalapril decreased systolic (166 ± 4 *v* 152 ± 5 mm Hg, $P < .05$) and diastolic (102 ± 2 *v* 95 ± 2 mm Hg, $P < .05$) blood pressure. Peripheral insulin sensitivity, ie, insulin stimulation of glucose utilization, increased approximately 30%, or by 4.3 ± 1.7 μmol/kg · min (13.1 ± 2.0 *v* 17.4 ± 3.5 μmol/kg · min, $P < .05$, 0 *v* 4 weeks) during enalapril treatment, but remained unchanged during placebo treatment (15.4 ± 2.8 *v* 15.3 ± 2.7 μmol/kg · min, respectively). The increase in glucose utilization during enalapril treatment was fully explained by an increase of 4.1 ± 1.7 μmol/kg · min in glucose storage (4.1 ± 1.2 *v* 8.1 ± 2.9 μmol/kg · min, $P < .05$) while glucose oxidation remained unchanged. High-density lipoprotein (HDL) cholesterol increased by 8% ($P < .05$) and hemoglobin A_{1c} (HbA_{1c}) improved slightly (7.7% ± 0.7% *v* 7.3% ± 0.7%, $P < .05$) in the enalapril group, but not in the placebo group. We conclude that enalapril improves insulin sensitivity by increasing glucose storage in hypertensive patients with NIDDM. These data indicate that the beneficial metabolic effects of angiotensin-converting enzyme (ACE) inhibitors are not restricted to nondiabetic patients, and that insulin resistance is partially reversible in hypertensive NIDDM patients.

ESSENTIAL HYPERTENSION,[1,2] non–insulin-dependent diabetes mellitus (NIDDM),[3] and hypertriglyceridemia[4] are associated with insulin resistance and hyperinsulinemia. Both hypertriglyceridemia[5] and hyperinsulinemia[6,7] are established and independent risk factors for coronary heart disease (CHD). It has been proposed that the smaller-than-predicted benefit of antihypertensive therapy on CHD incidence could be due to adverse metabolic effects of antihypertensive drugs. Specifically, both β-blockers and thiazide diuretics, the drugs most commonly used in trials examining the effect of antihypertensive medication on CHD incidence, induce insulin resistance and hypertriglyceridemia in nondiabetic[8] and diabetic patients.[9] As shown by Pollare et al,[10] these adverse effects have not been observed with angiotensin-converting enzyme (ACE) inhibitors in nondiabetic subjects with essential hypertension. Indeed, ACE inhibitors actually have been reported to enhance insulin sensitivity and to induce potentially antiatherogenic changes in blood lipids in patients with essential hypertension.[10]

In patients with NIDDM, recent data have suggested insulin resistance to be a partially familial, perhaps genetic rather than secondary phenomenon.[11,12] As in nondiabetic individuals, both insulin resistance[13] and hypertension[14] contribute to the twofold to threefold increase in CHD risk in NIDDM.[15] In hypertensive patients with NIDDM, insulin resistance may be more severe than in normotensive patients.[16]

Data are controversial regarding the effect of ACE inhibitors on insulin resistance in patients with NIDDM.[17,18] In the short-term study by Torlone et al.,[17] captopril increased whole-body glucose utilization by 30%[17] and doubled forearm glucose uptake.[19] In contrast, in a sequential single-blind study where 4 weeks of hydrochlorothiazide treatment was followed by 6 weeks of low-dose enalapril (10 to 20 mg) therapy, Prince et al[18] found no improvement in insulin sensitivity in hypertensive NIDDM patients. Whether this was due to a carryover effect of hydrochlorothiazide, the dose of enalapril, or the type of ACE inhibitor used is unclear. To resolve this issue, we performed a double-blind, placebo-controlled study using standard doses of enalapril to determine whether insulin resistance can be ameliorated in hypertensive patients with NIDDM.

SUBJECTS AND METHODS

The study consisted of a 4-week, single-blind run-in period and a 4-week, double-blind (placebo *v* enalapril) study period. Sixteen patients participated in the study. Their clinical characteristics are shown in Table 1. Groups were matched for hemoglobin A_{1c} (HbA_{1c}) levels (Table 1). The inclusion criteria were (1) NIDDM and hypertension (systolic blood pressure ≥160 mm Hg and diastolic blood pressure ≥95 mm Hg at least twice during the run-in period); (2) fasting C-peptide exceeding 0.33 nmol/l; (3) no history of insulin therapy; (4) weight-stable for 6 months before the study; (5) aged 35 to 70 years. Exclusion criteria were (1) diseases other than diabetes, abnormal liver, kidney, or thyroid function or serum cortisol; (2) history of myocardial infarction, unstable angina, or heart failure; (3) macroscopic proteinuria, elevated serum creatinine, proliferative retinopathy, or symptomatic neuropathy; (5) alcohol or drug abuse; and (6) pregnancy.

Antihypertensive treatment was withdrawn 4 weeks before the run-in period in all except two patients, whose medication (metoprolol, n = 1; diltiazem, n = 1) was continued unchanged. Five patients in the enalapril group and three patients in the placebo group were treated with oral hypoglycemic agents (sulfonylurea and metformin, n = 4; sulfonylurea only, n = 4), which were

From the Second and Third Departments of Medicine, University of Helsinki, Helsinki, Finland.

Submitted October 18, 1993; accepted April 7, 1994.

Supported by grants from the Finnish Academy of Science (H.Y.) and the Finnish Diabetes Research Foundation (H.Y.).

Address reprint requests to H. Vuorinen-Markkola, MD, Second Department of Medicine, Haartmaninkatu 4, SF-00290 Helsinki, Finland.

0026-0495/95/4401-0015$03.00/0

Table 1. Baseline Characteristics of the Patients

	Enalapril Group	Placebo Group
n (M/F)	4/4	6/2
Age (yr)	53 ± 3	57 ± 3
Duration of diabetes (yr)	8 ± 2	8 ± 2
Body mass index (kg/m²)	28 ± 1	30 ± 1
Waist to hip ratio	1.00 ± 0.01	0.98 ± 0.02
HbA_{1c} (%)*	7.7 ± 0.7	7.6 ± 0.2
Serum C-peptide (nmol/L)†	1.0 ± 0.1	1.0 ± 0.1
Urinary albumin excretion (μg/min)	8 ± 1	5 ± 2

*Reference range 4.0% to 6.0%.

†Reference range 0.3 to 0.7 nmol/L.

continued unchanged. The other eight patients were treated with diet alone. The weight of the patients was stable during the study.

During the 4-week run-in period, all subjects received one tablet of placebo per day. Blood pressure, HbA_{1c} (Fully Automated Glycosylated Hemoglobin Analyzer System, BioRad, Richmond, CA; reference range, 4.0% to 6.0%), serum free insulin (Phadeseph Insulin RIA kit, Pharmacia, Uppsala, Sweden; precipitation with polyethylene glycol[20]), triglyceride, total cholesterol (kits from Boehringer Mannheim, Mannheim, Germany[21]), high-density lipoprotein (HDL)[22] and low-density lipoprotein[23] cholesterol, creatinine, and electrolyte concentrations were determined at −4, −2, and 0 weeks. Insulin sensitivity measurements were performed at 0 and 4 weeks as detailed below. At 0 weeks, patients were randomly allocated to receive either enalapril (20 mg per day) or placebo (one tablet per day) for 4 weeks, and then were discharged from the hospital. The patients visited the outpatient clinic at 2 weeks for the same tests as during the run-in period. If the systolic pressure exceeded 180 mm Hg or diastolic pressure exceeded 90 mm Hg, the enalapril/placebo dose was doubled. This was instituted in four patients in the enalapril group and six patients in the placebo group.

The nature and potential risks of the study were explained to patients before they gave their voluntary consent to participate. The study protocol was approved by the Ethical Committee of the Helsinki University Central Hospital.

Insulin Sensitivity Measurements at 0 and 4 Weeks

Glucose production and utilization. For measurement of insulin sensitivity, patients were admitted to the hospital 1 day before the study. They ingested a diet containing 25 kcal/kg, with 55%, 30%, and 15% of the calories from carbohydrate, fat, and protein, respectively. The last meal was served at 7:30 PM.

At 4:00 AM, a primed-continuous intravenous infusion of [3-^{3}H]glucose (Amersham, Buckinghamshire, England) was started and continued until 11:00 AM to determine rates of glucose production and utilization in the basal state (−30 to 0 minutes, or 7:30 to 8:00 AM) and during hyperinsulinemia (0 to 180 minutes, or 8:00 to 11:00 AM). The priming dose was calculated as follows: priming dose (μCi) = 20 μCi × blood glucose (mmol/L)/5 mmol/L. The rate of the continuous infusion was 0.2 μCi/min. At −60 minutes (7:00 AM), a catheter was inserted retrogradely in a heated hand vein for sampling of arterialized venous blood.[24] Blood samples for measurement of glucose specific activity were taken from arterialized venous blood at −30, −15, 0, 120, 150, and 180 minutes.

To determine hepatic and peripheral insulin sensitivity, ie, the ability of insulin to suppress hepatic glucose production and stimulate glucose utilization, a primed-continuous infusion of insulin (Actrapid HM, Novo, Copenhagen, Denmark) was started at 0 minutes to increase and maintain plasma insulin at approximately 450 pmol/L.[24] Comparable plasma glucose and serum free-insulin concentrations were achieved in both groups at 0 and 4 weeks (Table 2). After starting the insulin infusion, the plasma glucose level (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA) was measured every 5 minutes in blood samples taken from arterialized venous blood. During the insulin infusion (0 to 180 minutes), plasma glucose was allowed to decrease until 120 minutes and was maintained constant thereafter (120 to 180 minutes) by a variable infusion of 20% glucose. The plasma free-insulin level was measured at −30, −15, 0, 30, 60, 90,

Table 2. Glucose Metabolism and Serum Lipid, Creatinine, and Electrolyte Concentrations in Enalapril and Placebo Groups

	Enalapril Group		Placebo Group	
	0 wk	4 wk	0 wk	4 wk
Glucose metabolism				
Plasma glucose, clamp (mmol/L)†	8.3 ± 0.9	7.9 ± 0.9	7.2 ± 0.5	7.1 ± 0.5
Plasma glucose, clamp (mmol/L)‡	6.7 ± 0.8	6.8 ± 0.8	5.6 ± 0.5	5.7 ± 0.5
Serum free-insulin, clamp (pmol/L)‡	432 ± 30	432 ± 54	414 ± 36	462 ± 36
Basal glucose utilization (μmol/kg · min)§	12.6 ± 1.4	11.0 ± 0.9	10.3 ± 1.2	10.3 ± 0.8
Basal glucose production (μmol/kg · min)§	13.1 ± 1.6	12.1 ± 0.8	10.2 ± 1.5	10.8 ± 0.9
Serum lipids				
Total cholesterol (mmol/L)	5.4 ± 0.3	5.4 ± 0.3	5.4 ± 0.3	5.3 ± 0.3
HDL	1.04 ± 0.08	1.12 ± 0.08*	1.07 ± 0.08	1.03 ± 0.09
LDL	4.03 ± 0.27	3.81 ± 0.23	3.93 ± 0.24	3.93 ± 0.25
Triglycerides, total	1.75 ± 0.31	2.13 ± 0.38	1.96 ± 0.43	1.65 ± 0.28
Serum creatinine and electrolytes				
Creatinine (μmol/L)	85 ± 4	85 ± 5	83 ± 3	86 ± 4
Potassium (mmol/L)	4.2 ± 01	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1
Sodium (mmol/L)	139 ± 1	139 ± 1	140 ± 1	140 ± 1
Urinary electrolyte excretion rate				
Potassium (μmol/min)	47 ± 6	50 ± 4	47 ± 6	53 ± 7
Sodium (μmol/min)	97 ± 16	109 ± 17	155 ± 19	161 ± 18

*$P < .05$ *v* 0 weeks.

†During the first 2 hours of the clamp (0 to 120 minutes).

‡During the last hour (120 to 180 minutes) of constant glycemia.

§Basal, measured after an overnight fast before start of insulin infusion.

120, 150, and 180 minutes. Serum ACE activity[25] and C-peptide concentration (RIA, the RIA-mat C-Peptide II kit, BYK-Sangtec Diagnostica, Frankfurt, Germany) were measured at 0 minutes. Urinary albumin, potassium, and sodium excretion were determined in urine collected over the 4-hour period (7:00 to 11:00 AM).

Rates of glucose production and utilization in the basal state (−30 to 0 minutes) and during hyperinsulinemia (120 to 180 minutes) were calculated using the non–steady-state equation of Steele[26] assuming a glucose distribution volume of 200 mL/kg and a pool fraction of 0.65. Under some conditions, the use of this model leads to underestimation of glucose production.[27] To minimize these errors, the [3-^{3}H]glucose infusion period was started at 4:00 AM and lasted 240 minutes instead of the usual 120 to 180 minutes before the insulin infusion was started. The total duration of the [3-^{3}H]glucose infusion was 7 hours (from 4:00 to 11:00 AM). The rate of glucose utilization was calculated from the glucose infusion rate plus residual hepatic glucose production.

Glucose oxidation and storage. To determine the rate of glucose oxidation, indirect calorimetry measurements were performed during the last hour of the insulin infusion (120 to 180 minutes) using a computerized flow-through canopy gas analyzer system (Deltatrac Metabolic Monitor, Datex, Helsinki, Finland) as previously described in detail.[28] The protein oxidation rate was estimated from urinary urea nitrogen excretion. Glucose storage or nonoxidative glucose utilization was defined as the difference between total and oxidative glucose utilization. The storage component of glucose utilization consists mainly of glycogen synthesis in patients with NIDDM.[29]

Blood Pressure Measurements

Blood pressure was measured between 8:00 and 10:00 AM in the sitting position after 5 to 10 minutes of rest from the same arm using a random-zero sphygmomanometer (The Random Zero Sphygomomanometer, Hawksley & Sons, Lancing, England).

Statistical Methods

Comparisons between 0- and 4-week study periods and between study groups were performed using paired and unpaired *t* test analyses. All data are shown as the mean ± SEM.

RESULTS

Blood Pressure, Serum ACE, Urinary Albumin Excretion

The pretreatment systolic (166 ± 4 *v* 165 ± 7 mm Hg, enalapril *v* placebo) and diastolic (102 ± 2 *v* 102 ± 3 mm Hg) blood pressures were comparable in the enalapril and placebo groups. In the enalapril group systolic blood pressure decreased to 152 ± 5 mm Hg ($P < .05$) and diastolic to 95 ± 2 mm Hg ($P < .05$). In the placebo group systolic (162 ± 8 mm Hg) and diastolic (100 ± 4 mm Hg) blood pressures remained unchanged. Serum ACE activities were comparable in the enalapril (49 ± 7 U/L) and placebo (66 ± 6 U/L) groups at randomization. Enalapril decreased serum ACE activity to 17 ± 4 U/L ($P < .005$), whereas there was no change in the placebo group (63 ± 6 U/L).

The urinary albumin excretion rate decreased from 8 ± 1 to 4 ± 1 μg/min ($P < .05$) in the enalapril group, but remained unchanged in the placebo group (5 ± 2 *v* 6 ± 2 μg/min, 0 *v* 4 weeks). Urinary sodium and potassium excretion rates and serum creatinine and electrolyte concentrations remained unchanged in both groups (Table 2).

Glucose Metabolism

Basal measurements. HbA_{1c} improved slightly in the enalapril group (7.7% ± 0.7% *v* 7.3% ± 0.7%, $P < .05$, 0 *v* 4 weeks), but not in the placebo group (7.6% ± 0.2% *v* 7.4% ± 0.2%, NS, respectively). Basal rates of glucose production and utilization remained unchanged during the treatment periods (Table 2).

Insulin sensitivity. Plasma glucose and serum free-insulin concentrations were comparable at all study occasions (Table 2). The rate of glucose utilization during insulin stimulation increased in the enalapril group by approximately 30%, or 4.3 ± 1.7 μmol/kg · min, from 13.1 ± 2.0 to 17.4 ± 3.5 μmol/kg · min ($P < .05$), but remained unchanged in the placebo group (15.4 ± 2.8 *v* 15.3 ± 2.7 μmol/kg · min, 0 *v* 4 weeks; Fig 1). The increase in glucose utilization with enalapril was due to an approximately 50% increase in glucose storage (4.1 ± 1.3 *v* 8.1 ± 2.9 μmol/kg · min, $P < .05$, 0 *v* 4 weeks). The increase in glucose utilization was not different between patients in whom the enalapril dose was 20 or 40 mg/d (data not shown). In the placebo group, glucose storage remained unchanged (6.7 ± 2.3 *v* 5.7 ± 2.0 μmol/kg · min, respectively). Rates of glucose oxidation were similar in enalapril (9.0 ± 0.9 *v* 9.2 ± 0.8 μmol/kg · min) and placebo (8.6 ± 1.2 *v* 9.6 ± 1.0 μmol/kg · min, respectively) groups. Endogenous glucose production, measured during the last hour of the insulin infusion, was not significantly different in the enalapril (4.6 ± 1.4 *v* 0.8 ± 1.5 μmol/kg · min, 0 *v* 4 weeks) and placebo (2.7 ± 1.6 *v* 1.4 ± 1.2 μmol/kg · min, 0 *v* 4 weeks) groups.

Serum Lipids

HDL cholesterol increased from 1.04 ± 0.08 to 1.12 ± 0.08 mmol/L ($P < .05$) in the enalapril group, but there was no change in the placebo group (1.07 ± 0.08 *v* 1.03 ± 0.09 mmol/L, NS, 0 *v* 4 weeks). Total and low-density lipoprotein cholesterol and serum triglycerides remained unchanged (Table 2).

DISCUSSION

The present data indicate that part of the insulin resistance in hypertensive patients with NIDDM is reversed

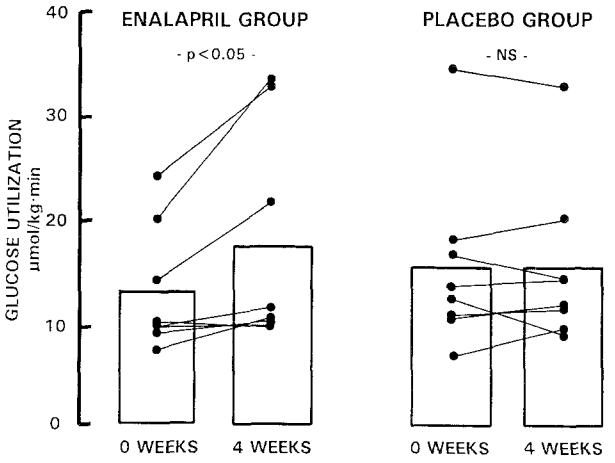

Fig 1. Rate of total glucose utilization during insulin stimulation at 0 and 4 weeks in enalapril and placebo groups.

during antihypertensive therapy with enalapril. Furthermore, we observed slight improvements in glycemic control, serum lipids, and urinary albumin excretion during 4 weeks of enalapril treatment. These data confirm the findings of Torlone et al,[17] who observed a 30% improvement in glucose utilization after 2 days of captopril therapy in hypertensive NIDDM patients. However, our findings contrast with those of Prince et al,[18] who found no change in insulin sensitivity when measured after 4 weeks of hydrochlorothiazide and again after 6 weeks of enalapril treatment in patients with NIDDM. The open, sequential study design used by Prince et al[18] differs from the present double-blind, parallel design and might provide an explanation for the different results. Also, in the latter study[18] two of the nine patients were on insulin therapy and thus were not completely comparable to our patients.

The increase in insulin sensitivity in the present study was due to an increase in glucose uptake rather than an improved suppression of hepatic glucose production by insulin. Under the conditions of the present insulin sensitivity measurements, the majority of glucose is taken up by muscle tissue.[29] In skeletal muscle, the rate of glucose uptake is in turn determined by the product of blood flow and the glucose arteriovenous difference. Recent data would indicate that impaired insulin stimulation of blood flow in skeletal muscle characterizes patients with NIDDM.[30] This defect might not explain all of the insulin resistance in NIDDM, but could be the component amenable to improvement by agents that increase blood flow.

Both in patients with essential hypertension[31] and in NIDDM,[32] ACE inhibitors increase blood flow in skeletal muscle by several mechanisms. These include a decrease in the concentration of angiotensin II, a potent vasoconstrictor,[33] and an increase in bradykinin,[32] which has vasodilating and insulin-like properties.[34,35] Furthermore, ACE inhibitors appear to decrease the production of noradrenaline in the vessel wall and the responsiveness of vascular smooth muscle to α-adrenergic vasoconstrictor stimuli.[33] Such alterations, provided they also occur in patients with NIDDM, might increase skeletal muscle blood flow and glucose uptake.

In the basal state, skeletal muscle depends on oxidation of free fatty acids for energy production.[36] Consequently, even if ACE inhibitors would increase blood flow during fasting, one would not expect to observe an increase in basal glucose utilization. Consistent with this, fasting plasma glucose and insulin remained unchanged in the present study. Also, basal hepatic glucose production remained unchanged, which is consistent with the exclusive use of free fatty acids by the liver in the basal state[37] and with the lack of an effect of ACE inhibitors on splanchnic blood flow.[31] The slight decrease in HbA_{1c} during enalapril therapy is thus likely to reflect improved postprandial glucose utilization rather than a change in basal glucose metabolism.

Low HDL cholesterol and high triglyceride concentrations are commonly observed in insulin-resistant conditions[38] and constitute a risk factor for CHD.[39,40] The small increase in HDL cholesterol in the present study thus might reflect improved insulin sensitivity. Enalapril also slightly decreased urinary albumin excretion, a change that could simply be a consequence of its antihypertensive effect or a drug effect that is independent of blood pressure.[41]

In conclusion, antihypertensive therapy with enalapril improves insulin-dependent glucose uptake in hypertensive patients with NIDDM. Given the known vasodilating effects of ACE-inhibitors and the impaired insulin-induced increase in blood flow in patients with NIDDM,[30] it is possible that ACE inhibitors reverse this hemodynamic component of insulin resistance in NIDDM. The failure to detect any significant increase in glucose oxidation is not incompatible with a predominant increase in blood flow. First, the rate of glucose oxidation in the present study (~ 9 μmol/kg · min) can be almost entirely explained by insulin-independent glucose oxidation in the brain (5.6 μmol/kg · min[42]) and by insulin-sensitive but presumably not-resistant glucose oxidation in the heart (2.8 μmol/kg · min[43-45]). Regardless of the mechanism underlying the improvement in insulin sensitivity by ACE inhibitors, the present data support the choice of ACE inhibitors as primary antihypertensive agents for patients with NIDDM, since they appear to have favorable effects on many CHD risk factors including hypertension,[14] insulin resistance,[13] and a low HDL cholesterol concentration.[39] Obviously, these short-term beneficial metabolic changes need to be tested in long-term prospective trials before the final role of ACE inhibitors for prevention of CHD can be assessed.

ACKNOWLEDGMENT

We thank Eero Helve for the pleasant cooperation, Elisa Kostamo and Riitta Kärkkäinen for their superb technical assistance in performing these studies, and the volunteers for their patience.

REFERENCES

1. Modan M, Halkin H, Almog S, et al: Hyperinsulinemia. A link between hypertension, obesity, and glucose intolerance. J Clin Invest 75:809-817, 1985

2. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 317:350-357, 1987

3. DeFronzo RA, Ferrannini E: The pathogenesis of non–insulin dependent diabetes. An update. Medicine 61:125-140, 1982

4. Yki-Järvinen H, Taskinen M-R: Interrelationships among insulin's antilipolytic and glucoregulatory effects and plasma triglycerides in nondiabetic and diabetic patients with endogenous hypertriglyceridemia. Diabetes 37:1271-1278, 1988

5. Frick HM, Elo O, Haapa K, et al: Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors and incidence of coronary heart disease. N Engl J Med 317:1237-1245, 1987

6. Pyörälä K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. Diabetes Care 2:131-141, 1979

7. Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. Diabetes Care 2:154-160, 1979

8. Houston MC: New insights and new approaches for the treatment of essential hypertension: Selection of therapy based on coronary heart disease risk factor analysis, hemodynamic profiles, quality of life, and subsets of hypertension. Am Heart J 117:911-951, 1989

9. Hypertension Detection and Follow-up Program Cooperative Group: Mortality findings for stepped-care and referred-care participants in the Hypertension Detection and Follow-up Program, stratified by other risk factors. Prev Med 14:312-335, 1985

10. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. N Engl J Med 321:868-873, 1989

11. Lillioja S, Mott DM, Zawadzki JK, et al: In vivo insulin action is familial characteristic in nondiabetic Pima Indians. Diabetes 36:1329-1335, 1987

12. Eriksson J, Franssila-Kallunki A, Ekstrand A, et al: Early metabolic defects in persons at increased risk for non–insulin-dependent diabetes mellitus. N Engl J Med 321:337-343, 1989

13. Pyörälä K, Laakso M, Uusitupa M: Diabetes and atherosclerosis: An epidemiologic view. Diabetes Metab Rev 3:463-524, 1987

14. Janka HU, Dirschedl P: Systolic blood pressure as a predictor for cardiovascular disease in diabetes. A 5-year longitudinal study. Hypertension 7:90-94, 1985 (suppl 2)

15. Kannel WB, McGee DL: Diabetes and cardiovascular disease. The Framingham Study. JAMA 241:2035-2038, 1979

16. Laakso M, Sarlund H, Mykkänen L: Essential hypertension and insulin resistance in non–insulin-dependent diabetes. Eur J Clin Invest 19:518-526, 1989

17. Torlone E, Rambotti AM, Perriello G, et al: ACE-inhibition increases hepatic and extrahepatic sensitivity to insulin in patients with type 2 (non– insulin-dependent) diabetes mellitus and arterial hypertension. Diabetologia 34:119-125, 1991

18. Prince MJ, Stuart CA, Padia M, et al: Metabolic effects of hydrochlorothiazide and enalapril during treatment of the hypertensive diabetic patient. Enalapril for hypertensive diabetics. Arch Intern Med 148:2363-2368, 1988

19. Jauch K-W, Hartl W, Guenther B, et al: Captopril enhances insulin responsiveness of forearm muscle tissue in non–insulin-dependent diabetes mellitus. Eur J Clin Invest 17:448-454, 1987

20. Desbuquois B, Aurbach GD: Use of polyethylene glycol to separate free and antibody-bound peptide hormones with radioimmunoassays. J Clin Endocrinol Metab 33:732-738, 1971

21. Wahlefeld AW: Triglycerides. Determination after enzymatic hydrolysis, in Bergmeyer HU (ed): Methods in Enzymatic Analysis (ed 2). New York, NY, Academic Press, 1974, pp 1831-1835

22. Finley PR, Schifman RB, Williams RJ, et al: Cholesterol in high-density lipoprotein: Use of Mg^{2+} dextran sulphate in its enzymatic measurement. Clin Chem 24:931-933, 1978

23. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

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

25. Harjanne A: Automated kinetic determination of angiotensin-converting enzyme in serum. Clin Chem 30:901-902, 1984

26. Steele R: Influences of glucose loading and of injected insulin on hepatic glucose output. Ann NY Acad Sci 82:420-430, 1959

27. Yki-Järvinen H, Consoli A, Nurjhan N, et al: Mechanism for underestimation of isotopically determined glucose disposal. Diabetes 38:744-751, 1989

28. Yki-Järvinen H, Puhakainen I, Saloranta C, et al: Demonstration of a novel feedback mechanism between FFA oxidation from intracellular and intravascular sources. Am J Physiol 260:E680-E689, 1991

29. Shulman GI, Rothman DL, Jue T, et al: Quantitation of muscle glycogen synthesis in normal subjects and subjects with non–insulin-dependent diabetes by ^{13}C nuclear magnetic resonance spectroscopy. N Engl J Med 322:223-228, 1990

30. Laakso M, Edelman SV, Brechtel G, et al: Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. Diabetes 41:1076-1083, 1992

31. Ventura HO, Frohlich ED, Messerli FH, et al: Immediate regional blood flow distribution following angiotensin converting enzyme inhibition in patients with essential hypertension. Am J Med 76:58-61, 1984

32. Kodama J, Katayama S, Tanaka K, et al: Effect of captopril on glucose concentration. Possible role of augmented postprandial forearm blood flow. Diabetes Care 13:1109-1111, 1990

33. Vanhoutte PM, Auch-Schwelk W, Biondi ML, et al: Why are converting enzyme inhibitors vasodilatators? Br J Clin Pharmacol 28:95S-104S, 1989 (suppl 2)

34. Dietze G: Modulation of the action of insulin in relation to the energy state in skeletal muscle tissue: Possible involvement of kinins and prostaglandins. Mol Cell Endocrinol 25:127-149, 1982

35. Jauch KW, Gunther B, Hartl W, et al: Improvement of impaired postoperative insulin action by bradykinin. Biol Chem Hoppe-Seyler 367:207-210, 1986

36. Andres R, Cader G, Zierler KL: The quantitatively minor role of carbohydrate in oxidative metabolism by skeletal muscle in intact man in the basal state. Measurements of oxygen and glucose uptake and carbon dioxide and lactate production in the forearm. J Clin Invest 35:671-682, 1956

37. Havel RJ, Kane JP, Balasse EO, et al: Splanchnic metabolism of free fatty acids and production of triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans. J Clin Invest 49:2017-2035, 1970

38. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

39. Castelli WP: Epidemiology of coronary heart disease: The Framingham Study. Am J Med 76:4-12, 1984 (suppl 2A)

40. Castelli WP: The triglyceride issue: A view from Framingham. Am Heart J 112:432-440, 1986

41. Marre M, Chatellier G, Leblanc H, et al: Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. Br Med J 297:1092-1095, 1988

42. Rowe GG, Maxwell GM, Castillo CA, et al: A study in man of cerebral blood flow and cerebral glucose, lactate and pyruvate metabolism before and after eating. J Clin Invest 38:2154-2158, 1959

43. Nuutila P, Koivisto VA, Knuuti J, et al: Glucose–free fatty acid cycle operates in human heart and skeletal muscle in vivo. J Clin Invest 89:1767-1774, 1992

44. Wisneski JA, Gertz EW, Neese RA, et al: Metabolic fate of extracted glucose in normal human myocardium. J Clin Invest 76:1819-1827, 1985

45. Nuutila P, Knuuti J, Ruotsalainen U, et al: Insulin resistance is localized to skeletal muscle but not heart muscle in type 1 diabetes. Am J Physiol 264:E756-E762, 1992