Improved Insulin Action and Glycemic Control After Long-Term Angiotensin-Converting Enzyme Inhibition in Subjects with Arterial Hypertension and Type II Diabetes

ELISABETTA TORLONE, MD
MARIELLA BRITTA, MD
ANNA MARIA RAMBOTTI, MD
GABRIELE PERRIELLO, MD
FAUSTO SANTEUSANIO, MD
PAOLO BRUNETTI, MD
GEREMIA B.BOLLI, MD

OBJECTIVE — To determine the long-term effects of the angiotensin-converting enzyme inhibitor captopril on insulin sensitivity in subjects with type II diabetes and arterial hypertension. The chronic effects of angiotensin-converting enzyme inhibition on insulin-sensitive individuals are presently controversial.

RESEARCH DESIGN AND METHODS — Sixteen subjects, with type II diabetes (on diet and/or diet plus oral hypoglycemic agents) and arterial hypertension, were studied. During a 1-mo run-in period no antihypertensive drugs were administered, but oral hypoglycemic agents were continued in subjects already in therapy. The subjects were then randomly assigned to two 3-mo treatment periods, with either captopril or placebo (single blind, cross-over design). At the end of each treatment period, insulin sensitivity was assessed by means of a euglycemic-hyperinsulinemic clamp (2 sequential steps, 2-h each, insulin infusion 0.25 and 1 mU · kg^{-1} · min^{-1}, steps 1 and 2, respectively), combined with infusion of [3-^{3}H]glucose (for calculation of hepatic glucose output and peripheral glucose utilization, rates of glucose disappearance), and indirect calorimetry (for calculation of glucose oxidation, nonoxidative glucose metabolism, and lipid oxidation). The percentage of HbA_{1c} was measured to assess long-term glycemic control.

RESULTS — Comparing data at the end of placebo and captopril treatment, captopril resulted in: lower blood pressure (systolic 154 ± 2 vs. 163 ± 3 mmHg and diastolic 93 ± 2 vs. 101 ± 2 mmHg); greater insulin sensitivity in hyperglycemic conditions (total amount of insulin infused and time of insulin infusion required to reach euglycemia, 1.73 ± 0.54 vs. 2.08 ± 0.60 U and 58 ± 8 vs. 70 ± 11 min, captopril and placebo, respectively, $P < 0.05$); greater insulin sensitivity in euglycemic conditions at liver level (hepatic glucose output 4.11 ± 0.55 vs. 5.2 ± 0.4 μmol · kg^{-1} · min^{-1}, step 1 of the clamp), muscle level (rates of glucose disappearance 26.1 ± 2.3 vs. 23.8 ± 2.1 μmol · kg^{-1} · min^{-1}, step 2 of the clamp), primarily attributable to ~29% increase in nonoxidative glucose metabolism, and adipose tissue level (plasma free fatty acid 0.185 ± 0.03 vs. 0.24 ± 0.02 mM and lipid oxidation 1.9 ± 0.3 vs. 2.21 ± 0.04 μmol · kg^{-1} · min^{-1} in step 1); and lower HbA_{1c} (6.7 ± 0.2 vs. 7.3 ± 0.2%, $P < 0.05$).

CONCLUSIONS — Long-term captopril administration in type II diabetic subjects improves insulin sensitivity in the postprandial state, not in the fasting state, and improves glycemic control.

From the Department of Internal Medicine and Endocrinological and Metabolic Sciences, University of Perugia, 06126 Perugia.

Address correspondence and reprint requests to Geremia B.Bolli, MD, Istituto di Medicina Interna e Scienze Endocrine e Metaboliche, Via E.Dal Pozzo, 06126 Perugia, Italy.

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Type II diabetes, non-insulin-dependent diabetes mellitus; BP, blood pressure; ACE, angiotensin-converting enzyme; OHA, oral antihyperglycemic agent; R_a, rate of glucose appearance; R_d, rate of glucose disappearance; FFA, free fatty acid; HPLC, high-performance liquid chromatography; HGO, hepatic glucose output; HGP, hepatic glucose production; G-STO, nonoxidative glucose metabolism; G-OX, glucose oxidation; L-OX, lipid oxidation; BMI, body mass index; FPG, fasting plasma glucose; CV, coefficient of variation; NEFA, nonesterified fatty acid; ANOVA, analysis of variance.

Type II diabetes and arterial hypertension are conditions of insulin resistance (1–6) frequently associated in the same subjects (7). Because arterial hypertension is an important cardiovascular risk factor for type II diabetic subjects, it is recommended that not only blood glucose, but also BP be meticulously controlled in subjects with both diabetes and hypertension (8). However, several widely used antihypertensive drugs, such as diuretics (9,10) and β-blockers (11,12), although effective in controlling hypertension, may exaggerate insulin resistance (9–12). Concerns have been voiced that these adverse metabolic effects may contribute to the progression of macrovascular disease, despite improved control of BP (13).

Recent studies indicate that acute administration of ACE inhibitors improves insulin action in nondiabetic and type II diabetic subjects, with or without hypertension (14–18). However, the long-term effects of ACE inhibitors on insulin action are far from being well established. In 3 studies, prolonged ACE inhibition resulted in improved insulin sensitivity (19–21), whereas in 3 different studies, no changes in insulin action were observed after long-term ACE inhibition (22–24). Although differences in experimental design and heterogeneity of subjects studied might explain the contrasting results, presently the long-term effects of ACE inhibition on insulin action and overall glycemic control in humans remain controversial.

Therefore, in view of the importance of this issue, these studies were undertaken to reassess the effects of long-term ACE inhibition on insulin action and overall glycemic control in subjects with type II diabetes and arterial hypertension.

RESEARCH DESIGN AND METHODS

— Sixteen subjects with mild arterial hypertension and type II diabetes, recruited from the outpatient clinic of the Department of Internal Medicine

Table 1—*Clinical characteristics of type II diabetic patients*

Patient no.	Age (y)	Sex (M/F)	BMI (kg/m^2)	FPG (mM)	HbA_{1c} (%)*	Sitting BP (mmHg)	Treatment	
							Diabetes	Hypertension
1	65	M	25	7	6.8	165/98	Diet	None
2	68	F	27.2	8.2	7.9	160/100	Glibenclamide	Diuretic
3	50	F	29	7.8	6.9	155/102	Diet	None
4	64	F	27.5	7.2	6.9	150/98	Diet	None
5	63	F	24	6.8	6.5	155/100	Diet	Metoprolol
6	52	F	25	7.2	7.7	160/98	Gliclazide	None
7	63	M	26.3	6.9	6.8	160/98	Diet	Diuretic
8	57	M	26.8	7	7.5	169/103	Glibenclamide	Diuretic
9	61	F	26.8	7.5	7.4	158/103	Glibenclamide	Metoprolol
10	65	M	26.3	7	6.9	170/104	Metformin	Diuretic
11	64	M	27	6.7	6.6	168/95	Diet	None
12	59	F	26	6.6	6.8	165/105	Metformin	Ca^+ channel blocker
13	61	M	27	7	8.2	162/102	Diet	None
14	63	F	27.6	7.4	7.5	165/100	Metformin	Diuretic
15	64	M	28.4	8	8.4	168/105	Gliclazide	None
16	60	M	27.7	7.6	8.1	170/100	Glibenclamide	None
Mean ± SE	61.2 ± 1.2	8M/8F	26.7 ± 0.3	7.24 ± 0.1	7.3 ± 0.2	163 ± 1.5/101 ± 0.7		

*Nondiabetic subjects' values are 4–5.8%.

and Endocrinological and Metabolic Sciences, University of Perugia, were studied after obtaining fully informed consent (Table 1). Apart from hypertension and type II diabetes, the subjects were healthy and apparently free of hypertension- and/or diabetes-related complications. On recruitment, the subjects were not on medications, with the exception of subjects 2, 5, 7–10, 12, and 14, who were on antihypertensive medications, and subjects 2, 6, 8–10, 12, 14, 15, and 16, who were on OHAs.

Study protocol

Institutional Review Board Committee approval was obtained for these studies. After an initial 4-wk run-in period—during which the antihypertensive therapy was withdrawn in subjects 2, 5, 7–10, 12, and 14, but diet and OHAs were continued in subjects 2, 6, 8–10, 12, 14, 15, and 16—baseline lying/standing BP and the percentage of HbA_{1c} were measured. The subjects were then randomly assigned two 3-mo treatment periods, with either captopril or placebo. This study was single blind (patient), with a cross-over design. The two treatment periods were separated by a 1-wk wash-out period, during which no antihypertensive therapy was given, while the OHAs, if any, were continued. In the captopril period, 12 subjects were started with an initial dose of 25 mg 2 times/day, whereas the remaining 4 subjects were given 50 mg 2 times/day. The dose of captopril was subsequently increased in 3 subjects, so that after the first 4 wk, 9 subjects were on 25 mg 2 times/day, and 7 were on 50 mg 2 times/day. Insulin sensitivity, as well as BP and HbA_{1c} were measured at the end of each treatment period. The subjects were asked to keep their diet, physical activity, and life-style as constant as possible throughout the study period.

Procedures

Insulin sensitivity was assessed in all patients by means of the euglycemic-hyperinsulinemic clamp technique (25,26), as described previously (16). In brief, the subjects were admitted to the Clinical Research Center of the Department of Internal Medicine and Endocrinological and Metabolic Sciences, University of Perugia, between 0630 and 0700, after an overnight fast (9–10 h). All subjects were given the therapeutic dose of captopril (but not OHA, if any), placed at bed rest, and maintained in the supine position throughout the experiments. To obtain arterialized venous blood samples (27), a hand vein was cannulated in a retrograde fashion with a 19-gauge butterfly needle and the hand maintained at 60–65°C in a thermoregulated plexiglass box. An antecubital vein of the contralateral arm was cannulated with an 18-gauge catheter needle. This line was used for infusion of insulin and glucose, both radioactive ([3-^{3}H]glucose) and nonradioactive (cold glucose). The venous and the arterialized venous lines were kept patent with an infusion of 0.9% NaCl at the rate of 0.5 ml/min by means of 2 peristaltic pumps (VM 8000 M, Vial Medical, St-Martin-Le-Vinoux, Grenoble, France).

Between 0700 and 0730, an in-

fusion of insulin (Actrapid HM U–40, Novo-Nordisk A/S, Denmark) diluted to 1 U/ml in 2 ml of the subject's whole blood and 0.9% NaCl to a final volume of 100 ml was started by means of a syringe pump (Harvard Apparatus, Ealing, South Natick, MA). This gradually decreased the plasma glucose concentration from the patient's hyperglycemic values to normal plasma glucose (4.5–5.5 mM) based on a previously described algorithm (28). Between 0900 and 0930, when plasma glucose concentration reached the target value of ~5 mM, the insulin infusion was stopped, and a primed (25 μCi) continuous infusion (0.25μCi/min) of [3-^{3}H]glucose (New England Nuclear, Boston, MA) was initiated and maintained throughout the studies for isotopic determination of rates of R_a and R_d. Three hours were allowed for isotopic equilibration, after which baseline blood samples were taken. During this period the subjects remained spontaneously euglycemic, and no insulin was infused. The euglycemic-hyperinsulinemic clamp was started between 1200 and 1230. Insulin was infused at the rate of 0.25 $mU \cdot kg^{-1} \cdot min^{-1}$ during the initial 2 h (0–120 min, low-dose insulin step, henceforth referred to as step 1) and at the rate of 1 $mU \cdot kg^{-1} \cdot min^{-1}$ during the following 2 h (121–240 min, high-dose insulin step, henceforth referred to as step 2).

During both steps of insulin infusion, cold glucose (20% solution) was infused at a variable rate to maintain plasma glucose concentration at ~5 mM, according to the principles of the glucose clamp technique (25,26). Substrate oxidation and energy expenditure were measured in all subjects by indirect calorimetry (29). Ninety minutes before the beginning of insulin infusion a transparent, plastic ventilated hood was placed over the subject's head and made airtight around the neck. Gas-exchange measurements were taken during a 45-min basal period after the subjects had adapted to the hood and stabilized their breathing pattern. Measurements were repeated during the last 45 min of steps 1 and 2 of clamp.

Analytical procedures

Arterialized venous blood samples were collected at 5- to 10-min intervals and assayed for glucose (determined at bedside by means of a Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA), glucose specific activity (30), insulin (31), C-peptide (32), and NEFAs by a colorimetric method using a kit (Wako Chemicals GmbH, Neuss, Germany), by previously described methods. For indirect calorimetry, air flow, O_2, and CO_2 concentrations in the expired and inspired air were measured by a computerized continuous open-circuit system (Deltatrac, Datex Instruments, Helsinki, Finland) (33). Air flow was measured by the air-dilution method, CO_2 concentration by a conventional infrared detector, and O_2 concentration by a fast differential paramagnetic O_2 sensor. The monitor has a precision of 2.5% for O_2 consumption and 1.0% for CO_2 production. Protein oxidation was estimated from urinary excretion of urea before and during the hyperinsulinemic-hyperglycemic clamp studies. Urine was collected immediately before the initiation of the isoglycemic-hyperinsulinemic clamp studies and then from the onset to the end of each study period for determination of glucose and nitrogen excretion, the latter measured by the method of Kjeldahl (34). The percentage of HbA_{1c} was measured by an HPLC method (35).

Calculations

R_a and R_d were calculated during the last 30 min of the basal period and throughout each of the 2 steps of the hyperinsulinemic-euglycemic clamp by using the non–steady-state equations of De Bodo et al. (36); rates were smoothed according to the method of Miles et al. (37). The infusion rate of cold glucose was integrated over 30-min intervals and subtracted from the total R_a to obtain HGO. Negative numbers for HGP were observed only in step 2 of the clamp (1 $mU \cdot kg^{-1} \cdot min^{-1}$). As recently demonstrated on theoretical as well as experimental grounds (3), such an underestimation of glucose turnover by the tracer method is largely accounted for by a model error emerging at high rates of glucose metabolism.

Total body glucose metabolism was calculated by adding the mean rate of HGP (if a positive number) during the last 30 min of the baseline period and step 1 of the clamp studies to the mean glucose infusion rate during the same period, as reported previously (16,39), after subtracting the possible urinary glucose losses. However, in these studies glycosuria did not occur in any of the subjects. G-STO was calculated as the difference between total body glucose uptake and G-OX, as determined by indirect calorimetry.

Oxidation rates for carbohydrates, fat, and protein were calculated from the measured O_2 consumption, CO_2 production, and urinary nitrogen excretion adjusted for changes in plasma concentration of urea nitrogen (40), as reported previously (41). Whole body net L-OX is expressed in molar units by using the molecular weight of palmitate (M_r = 256). Estimated portal plasma insulin levels were calculated based on previously reported equations (42) where the endogenous insulin secretory rate was calculated based on a two-compartment model (43).

Statistical analysis

Data are given as means ± SE, and the statistical significance was evaluated using ANOVA for cross-over design studies corrected for repeated measures. Regressions were calculated using the least-square method (44).

RESULTS

BMI, glycemic control, and BP

After a 3-mo treatment, BMI after captopril was no different as compared with

that after placebo (26.9 ± 0.4 vs. 26.6 ± 0.3 kg/m^2, respectively) and the run-in period (NS). HbA_{1c} decreased slightly, but significantly by ~0.6% after captopril as compared with placebo (6.7 ± 0.2 vs. 7.3 ± 0.2%, respectively, $P = 0.05$). Arterial BP was lower after captopril than after placebo (sitting, systolic 154 ± 2 vs. 163 ± 3 mmHg; diastolic 93 ± 2 vs. 101 ± 2 mmHg, respectively, $P < 0.005$). In 11 subjects, BP was 164 ± 3/102 ± 2 mmHg after placebo and 152 ± 3/91 ± 2 mmHg after captopril (henceforth referred to as responders), whereas in the remaining 5 subjects it did not change significantly after captopril as compared with placebo (160 ± 3/98 ± 2 vs. 162 ± 3/99 ± 3 mmHg, respectively, NS). These 5 subjects henceforth will be referred to as nonresponders.

Baseline FPG and insulin concentrations

On the morning of the study, before the intravenous insulin infusion, FPG (8.8 ± 0.4 vs. 9.1 ± 0.35 mM) and insulin concentrations (63.3 ± 6.2 vs. 59.2 ± 5.3 pM) after a 3-mo treatment with captopril and placebo, respectively, were not different. The total amount of insulin infused intravenously and the time required to normalize plasma glucose concentration after captopril (1.73 ± 0.54 U and 58 ± 8 min) were less than those after placebo (2.08 ± 0.6 U and 70 ± 11 min) ($P < 0.05$). During the following 3-h equilibration period during which no insulin was infused (−3 h–0 h), mean plasma glucose concentrations in the captopril and placebo were not different (5.4 ± 0.1 vs. 5.05 ± 0.1 mM, respectively).

Insulin sensitivity

Baseline plasma insulin concentrations in the captopril and placebo study (58.4 ± 8.15 vs. 50.3 ± 7 pM) were similar. During the insulin infusion, plasma insulin increased to similar plateau concentrations in steps 1 and 2 in the captopril (150.5 ± 9 vs. 500 ± 28

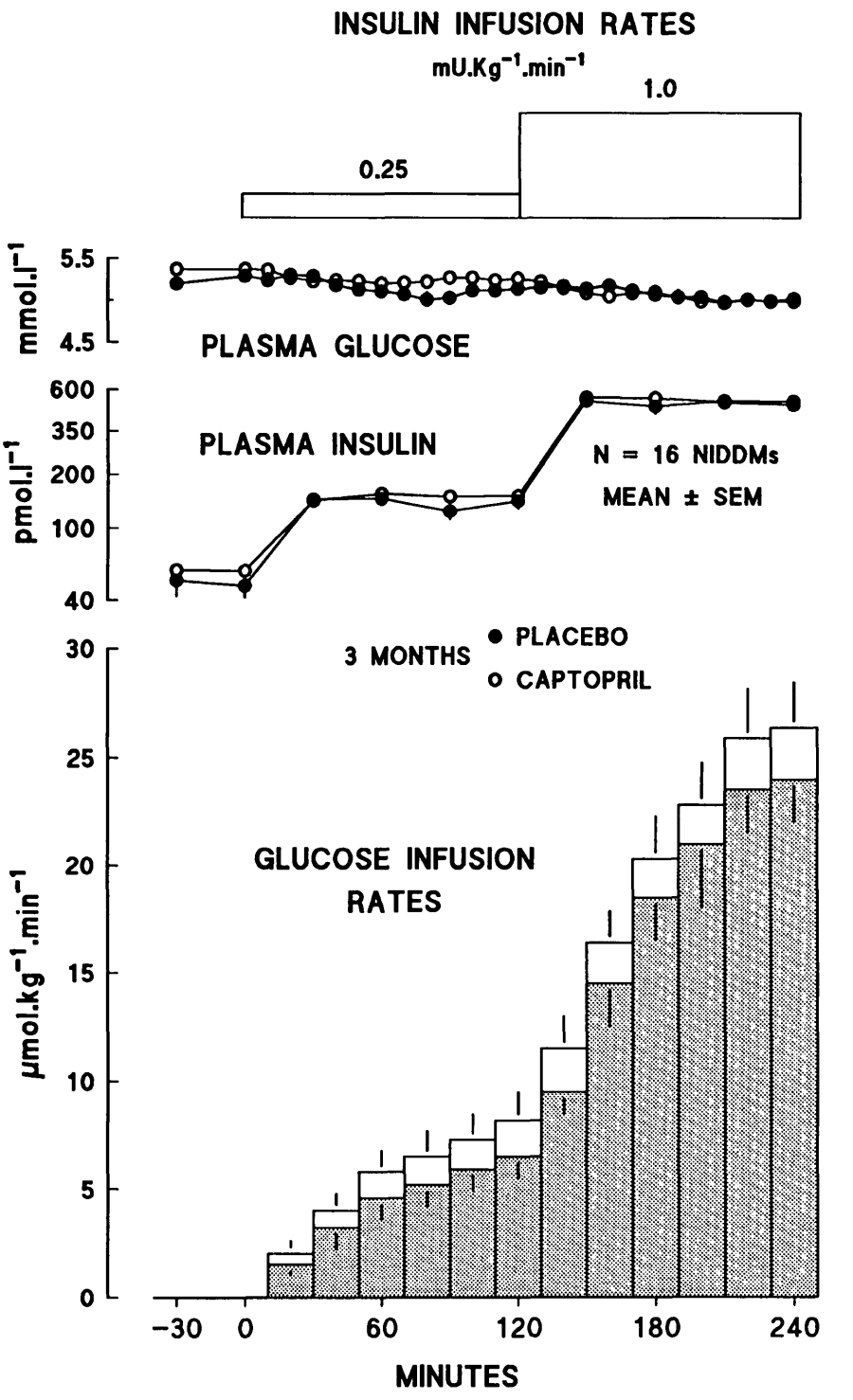

Figure 1—*Plasma glucose, insulin concentrations, and rates of glucose infusion required to keep euglycemia during two-step hyperinsulinemia in 16 type II diabetic subjects studied after a 3-mo treatment with captopril or placebo.*

pM, respectively) and placebo (133 ± 13 vs. 517 ± 42 pM, respectively) study. As a result of exogenous glucose infusion, plasma glucose concentration was maintained at similar concentrations in the captopril and the placebo study (5.15 ± 0.05 vs. 5.1 ± 0.04 mM, respectively) (CV of plasma glucose <5%). Baseline plasma C-peptide concentration was similar in the captopril and placebo studies and suppressed to similar values during the clamp study on both occasions (NS, data not shown). Similarly, estimated plasma portal insulin concentrations were similar during baseline and steps 1 and 2 in the captopril (187 ± 11.3, 266 ± 18, and 547 ± 28, respectively) and placebo studies (185 ± 10, 260 ± 20, and 550 ± 28, respectively) (baseline, step 1, and step 2, respectively, NS) (Fig. 1).

The rate of glucose infusion required to maintain euglycemia was greater after captopril than after placebo, both in step 1 of the clamp study (7.41 ± 0.8 vs. 6.15 ± 0.7 μmol · kg^{-1} · min^{-1}, respectively) as well as in step 2 (26.1 ± 2.3 vs. 23.7 ± 2.1 μmol · kg^{-1} · min^{-1}, respectively) ($P < 0.05$). A correlation was observed between improved insulin sensitivity in the clamp studies and a decrease in the percentage of HbA_{1c} ($r = 0.63$, $P < 0.05$).

R_a and R_d

Baseline R_as (HGP) were similar after captopril and placebo (Fig. 2). Following initiation of the hyperinsulinemic-euglycemic clamp, captopril treatment resulted in a greater suppression of HGP compared with placebo, both in step 1 (4.11 ± 0.55 vs. 5.20 ± 0.4 μmol · kg^{-1} · min^{-1}, respectively) and step 2 (−1.8 + 0.2 vs. −0.7 μmol · kg^{-1} · min^{-1}, respectively, $P < 0.05$). However, in this last step, negative numbers of HGP were obtained, as reported previously (15,36,37).

Baseline rates of peripheral glucose utilization were similar in the captopril and placebo studies and did not increase in step 1 of the clamp study. However, captopril resulted in a greater stimulation of peripheral glucose utilization in step 2 of the clamp study (26.1 ± 2.3 vs. 23.75 ± 2.1 μmol · kg^{-1} · min^{-1}, captopril vs. placebo, respectively, $P < 0.05$).

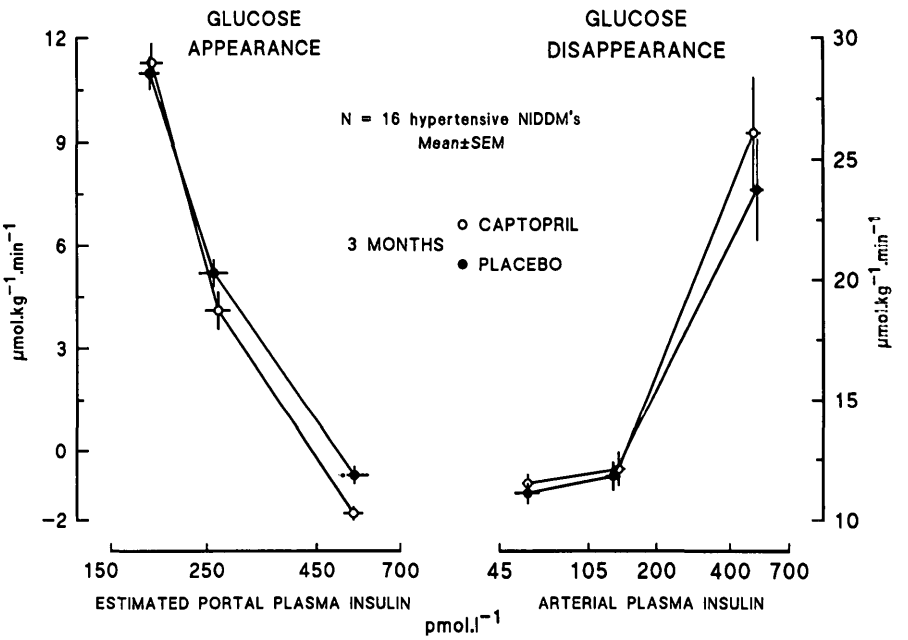

Figure 2—*R_a and R_d during two-step hyperinsulinemia in 16 type II diabetic subjects studied after a 3-mo treatment with captopril or placebo.*

Rates of G-OX and G-STO

Rates of G-OX were not affected by captopril, neither at baseline nor in steps 1 and 2 of the clamp. However, captopril resulted in an increased rate of G-STO in step 2 of the clamp (14.5 ± 1.8 vs. 11.2 ± 1.6 μmol · kg^{-1} · min^{-1}, captopril vs. placebo, $P < 0.05$) (Fig. 3).

Plasma FFA concentration and rates of L-OX

Before the hyperinsulinemic-euglycemic clamp, plasma FFAs were no different in the captopril and placebo studies (0.55 ± 0.04 vs. 0.51 ± 0.5 mM, respectively, NS). However, in step 1 of the clamp, plasma FFAs were more suppressed after captopril compared with placebo (0.185 ± 0.03 vs. 0.24 ± 0.02 mM, respectively, $P < 0.05$), whereas in step 2, plasma FFAs were maximally suppressed on both occasions (Fig. 4).

Baseline L-OX was similar in the two treatment periods. L-OX was more suppressed after captopril than after placebo in step 1 of the clamp (1.90 ± 0.04 vs. 2.21 ± 0.04 μmol · kg^{-1} · min^{-1}, respectively, $P < 0.05$), whereas it was suppressed to a similar extent after the two treatment periods in step 2.

Correlations between BP and insulin sensitivity and between plasma FFAs and glucose turnover rates

No correlations were observed between changes in arterial BP, insulin sensitivity of glucose, and lipid metabolism, neither after placebo nor after captopril.

Similarly, no correlations were found between the suppression of plasma FFAs or L-OX and the rate of HGP or the rate of glucose utilization, neither after placebo nor after captopril.

CONCLUSIONS— This study indicates that long-term treatment of arterial hypertension of type II diabetic subjects

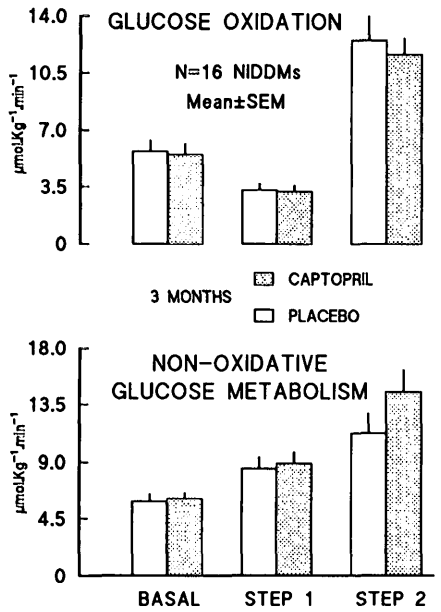

Figure 3—*Rates of G-OX and G-STO during two-step hyperinsulinemia in 16 type II diabetic subjects studied after a 3-mo treatment with captopril or placebo.*

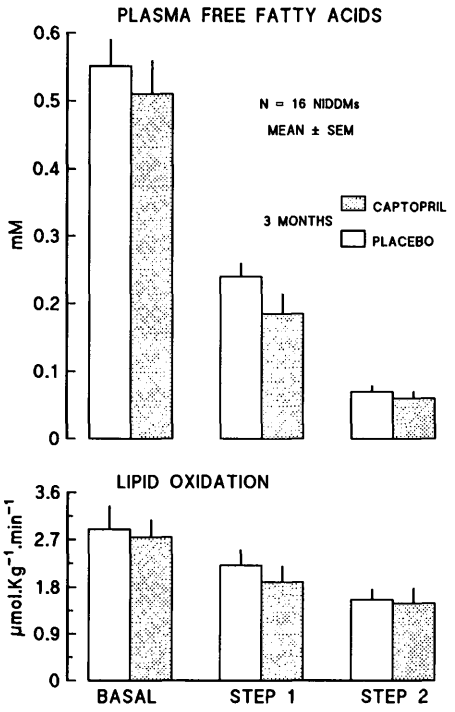

Figure 4—*Plasma FFA during two-step hyperinsulinemia in 16 type II diabetic subjects studied after a 3-mo treatment with captopril or placebo.*

with the ACE inhibitor captopril reduces BP and at the same time improves insulin action both in hyperglycemic and euglycemic conditions. The greater insulin sensitivity observed in these studies during captopril treatment occurred in euglycemic conditions at the level of all the target organs of insulin action, i.e., the liver, where glucose production was decreased by ~20% (from 5.6 ± 0.6 to 4.1 ± 0.55 $\mu mol \cdot kg^{-1} \cdot min^{-1}$); the muscle, where insulin-mediated glucose utilization was increased by ~10% (from 23.8 ± 2.1 to 26.1 ± 2.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$); and the adipose tissue, as indicated by the ~8% decrease in plasma FFA concentration (from 0.24 ± 0.02 to 0.185 ± 0.03 mM), and by the ~12% decrease in the overall L-OX rate (from 2.21 ± 0.4 to 1.90 ± 0.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$).

Improved insulin sensitivity after captopril also occurred under hyperglycemic conditions, as indicated by the lower amount of insulin (1.73 ± 0.54 vs. 2.08 ± 0.6 U) and the shorter time of insulin infusion (58 ± 8 vs. 70 ± 11 min) (both $P < 0.05$) required to normalize FPG concentration before the hyperinsulinemic clamp. Additionally, in these studies captopril treatment resulted in a significant improvement in HbA_{1c} from 7.3 ± 0.2 to 6.7 ± 0.2%, which was correlated with the increased insulin sensitivity demonstrated in the clamp studies. This last finding indicates that the improved insulin action after captopril exerted a modest, but continuing beneficial effect on overall glycemic control. Thus, the results of these long-term studies corroborate and expand previous findings of improved insulin sensitivity in type II diabetic subjects after acute or short-term administration of ACE inhibitors (14–18).

Note that in this study the beneficial effects of ACE inhibition on insulin action did not occur at the low plasma insulin concentrations of the postabsorptive state, but rather at the high plasma insulin concentrations in step 2 of the clamp study (~500 pM), which mimics postprandial plasma insulin values. Translated into practical terms, this result would predict that long-term ACE inhibition should not affect postabsorptive glucose homeostasis in subjects with type II diabetes, but it should improve their prandial glucose tolerance. In these studies, this hypothesis is supported by the observation of a decrease in the percentage of HbA_{1c} after a 3-mo captopril treatment. Because FPG concentration did not decrease, postmeal blood glucose concentrations must sometimes have decreased to explain the lower percentage of HbA_{1c} observed after captopril.

The results of this study are in agreement with those of Paolisso et al. (19) and Vuorinen-Markkola et al. (21). The latter reported an improvement in insulin sensitivity in subjects with type II diabetes and hypertension after a 4-wk treatment with enalapril. In their double-blind, placebo-controlled study (21), ACE inhibition resulted in a marked (~33%) increase in the rate of glucose utilization under conditions of hyperinsulinemia and euglycemia comparable with those of this and previous studies (16). Interestingly, in the study by Vuorinen-Markkola et al. (21), the increase in insulin sensitivity after ACE inhibition was of a similar magnitude to that reported in previous acute studies (16). Also in addition, the percentage of HbA_{1c} decreased from 7.7 ± 0.7 to 7.3 ± 0.7% ($P < 0.05$), after long-term ACE inhibition in that study (21), as it did in these studies.

On the other hand, the results of this study are at variance with those of Seghieri et al. (24) who reported no beneficial effects of long-term ACE inhibition on insulin action and glucose tolerance in type II diabetic subjects with arterial hypertension. The differences in the experimental design of these studies likely account for the opposite conclusions in the studies by Seghieri et al. (24) as compared with this and other studies (20,

21). Seghieri et al. (24) reported in their diabetic subjects treated for 3 mo with captopril, a decrease in HbA_{1c} of ~0.4%, which they defined as statistically nonsignificant. However, because the study by Seghieri et al. (24) was not placebo controlled, an effect of captopril on overall glycemic control cannot be totally excluded. Moreover, Seghieri et al. (24) concluded that insulin sensitivity did not improve after captopril. However, it should be noted that Seghieri et al. (24) used an infusion of somatostatin, insulin, and glucose in fixed amounts to estimate insulin sensitivity. This test resulted in concentrations of plasma insulin of ~300 pM and plasma glucose of ~15 mM. Under these conditions, whole body glucose utilization is greatly stimulated (45) and glycosuria occurs. Clearly, under the experimental conditions used by Seghieri et al. (24), it would be quite difficult to demonstrate a further increase in glucose utilization after captopril because of the already rather high basal glucose utilization, unless captopril were a really powerful agent capable of stimulating glucose metabolism. However, it appears in these studies that the order of magnitude of improvement in insulin action during long-term treatment with captopril is ~15% (averaging the hepatic and muscular effects). This effect was too weak to be picked up in the test of insulin sensitivity used by Seghieri et al. (24). Finally, one important difference between the studies by Seghieri et al. (24) and these studies is that the ACE inhibitor captopril was not administered on the morning of the study day before the test in the studies of Seghieri et al. (24), whereas it was administered in our studies. Because of the short duration of action of captopril on ACE inhibition (46), it is also possible that its effects on insulin action are short-lived.

In these studies, long-term ACE inhibition improved insulin action at the level of the liver, muscle, and adipose tissue. Although effects of ACE inhibitors on insulin-mediated glucose utilization have been reported previously (20, 21), to the best of our knowledge this is the first study describing an improved insulin sensitivity at the level of the liver and adipose tissue—both playing an important role in the homeostasis of postmeal glucose tolerance (4,47). Regarding the effect of captopril on insulin-mediated glucose utilization, in these studies this effect was entirely caused by improved G-STO, i.e., primarily storage and not G-OX. Thus, captopril, and other ACE inhibitors (21), appear to interact with the key feature of insulin resistance in type II diabetes, i.e., reduced glucose storage in the muscle (1).

The mechanisms by which ACE inhibitors improve insulin action in short- (14–18) and long-term studies (20,21 and these studies) remain speculative. It might be a metabolic effect caused by the ACE inhibitor itself or mediated by greater tissue concentrations of bradikinins (48). The alternative explanation might be a hemodynamic effect, i.e., an increase in blood flow (49), which would deliver greater amounts of glucose and insulin to the target organs, especially in the prandial state (50). Regardless of the mechanism(s) involved, it appears that ACE inhibitors only influence insulin sensitivity when two conditions occur at the same time, namely the bioavailability of ACE inhibitor in plasma and increased plasma insulin concentration. In this respect, it would be important to avoid use of long-acting sulfonylureas drugs, which cause inappropriate hyperinsulinemia between meals (51) in subjects with type II diabetes taking ACE inhibitors for their hypertension, and to prefer short-acting sulfonylureas or multiple daily insulin injections. In fact, it is likely that the several cases of hypoglycemia reported (14,52,53) shortly after initiation of therapy with ACE inhibitors were caused by potentiation of action of inappropriate hyperinsulinemia attributable to an excess dose of sulfonylureas by ACE inhibitors.

In conclusion, these studies indicate that long-term administration of the ACE inhibitor captopril in type II diabetic subjects with arterial hypertension improves insulin action both in hyperglycemic (total amount of insulin infused and time of infusion of insulin required to normalize fasting plasma glucose concentration) and euglycemic condition (clamp data) and in overall glycemic control. Such a beneficial effect on glucose metabolism is quantitatively modest and might be considered as irrelevant by some clinicians (54). Nevertheless, the demonstration that ACE inhibitors improve long-term insulin sensitivity, in this and other studies (20,21), is important for two reasons. First, because hyperinsulinemia is considered a cardiovascular risk factor (6,55,56) and any therapeutic measure that reverses it, even partially, should be prefereble to other therapeutic agents such as diuretics and β-blockers, which deteriorate insulin action (9–12). Second, care should be taken to prevent interprandial hyperinsulinemia when long-acting sulfonylureas are used in type II diabetic subjects given ACE inhibitors, because of the risk of hypoglycemia. This problem can be easily approached by frequent home blood glucose monitoring after initiation of the ACE-inhibitor therapy and consequent adjustment of sulfonylurea dose.

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