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Insulin sensitivity in normotensive subjects during angiotensin converting enzyme inhibition with fosinopril*

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Summary. The effect of the new ACE-inhibitor, fosinopril, on insulin sensitivity (S_I), glucose homoeostasis and lipid profile has been examined in 24 young, healthy, normotensive men. S_I, fasting plasma glucose and insulin, serum total triglycerides (Tg) and lipoprotein cholesterol (C) fractions, and ACE activity were assessed after subjects had taken placebo for 1 week and after 3 further weeks either on placebo (12 subjects) or fosinopril 20 mg daily (12 subjects), administered in a double-blind, randomized order. Measurements were made after 3 days on a standard diet (2500 kcal/d, 45% carbohydrates, 40% fat and 15% proteins) and after an overnight fast.

Compared with control values at the end of the run-in placebo phase, fosinopril reduced plasma ACE activity (from 106 to 24 $nmol \cdot ml^{-1} \cdot min^{-1}$), Significantly increased plasma potassium and lowered upright systolic blood pressure. It also improved the k-value of the glucose disappearance rate after glucose load (from –1.70 to –1.88 $\% \cdot min^{-1}$) and tended to increase S_I slightly although not significantly (from 10.2 to $12.0 \cdot 10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$). Fasting plasma glucose, insulin, serum total, high-, low-, and very-low density lipoprotein cholesterol fractions and total triglycerides were unchanged following fosinopril and placebo.

The findings indicate that in healthy lean humans, ACE inhibition with fosinopril is neutral with regard to lipoprotein and carbohydrate metabolism, and that it may slightly enhance cellular glucose disposal. This calls for further evaluation in individuals at high risk of developing insulin resistance and in patients with impaired insulin sensitivity related to hypertension, obesity, decreased glucose tolerance and diabetes mellitus.

Key words: Insulin, Fosinopril; insulin sensitivity, glucose tolerance, lipoproteins, ACE inhibition, normal humans, blood pressure, adverse effects

The sensitivity of tissues to insulin is of physiological, pathophysiological and therapeutic relevance. The magnitude of and the response to insulin jointly determine the maintenance of metabolic equilibrium, and they modulate lipoprotein metabolism [1], the growth and migration of vascular smooth muscle cells [2, 3] and, under certain pathophysiological conditions, they probably also affect the blood pressure [4, 5]. The frequent association of impaired insulin sensitivity, hyperinsulinaemia, altered carbohydrate and lipoprotein metabolism, and certain cardiovascular disorders [6] demonstrates the intimate interrelationship of these factors.

Angiotensin converting enzyme (ACE) inhibitors have found widespread use in the treatment of hypertension [7, 8], particularly in hypertensive diabetics [9, 10] and patients with heavy proteinuria [11], and for the possible prevention or retardation of renal dysfunction [12]. Captopril and enalapril do not appear to alter fasting or post-glucose-load plasma glucose or insulin concentrations, or serum lipoproteins, in nondiabetic [7, 31] and insulin-dependent and non-insulin-dependent diabetic patients [9, 10]. Captopril slightly improved the insulin responsiveness of the tissues in some non-insulin-dependent diabetic patients [13] and insulin sensitivity in nondiabetic, essential hypertensive patients [14]. Fosinopril is a new, potent, long-acting ACE inhibitor, that can be given once daily [15]. It is a prodrug ester, which is rapidly hydrolyzed to the active phosphinic diacid form following systemic administration. Unlike captopril, it contains a phosphorus group, which plays an important role in specific binding to ACE, but no sulphhydryl group. Excretion of fosinoprilate, unlike that of other ACE inhibitors, is balanced via biliary and renal mechanisms [15].

A randomized, double blind, placebo-controlled study was designed to investigate the influence of fosinopril on

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insulin sensitivity, plasma insulin and glucose and lipoprotein composition in normal humans.

Material and methods

Subjects

The study group consisted of 24 young [25 (1) y, mean (SEM)] healthy, normotensive men. None had a family history of diabetes mellitus in first degree relatives. All were nondiabetic volunteers in excellent physical and mental condition, and their blood pressure consistently was < 140/90 mm Hg; they were all lean with a body mass index (BMI) of less than 25 $kg \cdot m^{-2}$ [22.6 (0.3) $kg \cdot m^{-2}$], and their waist to hip ratio ranged from 0.70 to 0.92 [0.84 (0.01)]. None was taking any drugs. Information on the family history of diabetes mellitus in parents and any siblings was obtained by direct questioning of the subjects and from their family doctors. Each subject provided written informed consent, and the study was approved by the local Ethics Committee.

At enrolment all subjects underwent routine clinical examination and were given a placebo tablet to be taken once daily at 08.00 h. One week later, the subjects were randomly allocated to receive a matched tablet containing either placebo or 20 mg of the ACE inhibitor, fosinopril, for a further 3 weeks.

Insulin sensitivity and other variables were assessed at the end of the run-in placebo phase and after the consecutive placebo or active drug phase. The subjects followed a standardized diet [16], containing 2500 kcal, with 45 % carbohydrate, 40 % fat and 15 % protein, for 3 days before each study day. No alcohol was ingested during that period. Sodium intake was also standardized at 160 mmol daily, and 24 h urine specimens were collected to monitor compliance. None of the subjects engaged in heavy physical activity on the day before the study; caffeine and smoking were avoided that least 12 h before the tests. Supine (10 min) and upright (2 min) blood pressure and heart rate were recorded at weekly intervals throughout the study.

Subjective adverse effects were assessed by open questioning after the run-in placebo and during the consecutive treatment phases.

Procedures

The subjects entered the research unit after an overnight fast of 12 h. They emptied the bladder for completion of the 24 h urine collection, and body weight was recorded. Thereafter, the subjects remained supine throughout the entire procedure. Insulin sensitivity was assessed dynamically by the minimal model approach [17, 18], with the use of the modified frequent sampling intravenous glucose tolerance test (FSIGT) [19]. Intravenous cannulas were placed in an antecubital vein in each arm. One was used for the injection of glucose and tolbutamide (the latter enhances the correlation of this model with the euglycaemic clamp technique [17]). Blood was sampled from the cannula in the contralateral arm, which was kept patent with a slow saline drip (1.0 $ml \cdot min^{-1}$). After needle placement, 30 min rest were allowed for resumption of basal conditions. Basal samples were taken at –20 and –10 min; at 08.45 h (t = 0) the modified FSIGT was begun by injection of 50 % D-glucose (300 $mg \cdot kg^{-1}$ body weight), administered steadily over 60 s. At t = 20 min, 300 mg tolbutamide (Orinase^R Diagnostic, The Upjohn Co., Kalamazoo, Michigan) was injected in to the same vein. Post-injection samples (4 ml) were collected over 180 min, according to the modified FSIGT protocol [19]. Venous blood samples for the determination of haemoglobin, haematocrit, white blood cell and platelet counts, serum lipids and lipoprotein fractions, plasma ACE activity, sodium, potassium, creatinine, urea, total protein and albumin were collected at t = –20 min.

Analytical methods

Radioimmunoassays of plasma insulin were performed in duplicate, using guinea pig antiporcine insulin antibody (NOVO Biolabs, Sweden) and ^{125}I porcine insulin as tracer in a working buffer of 12.1 g Tris · HCl pH 7.4, 0.2 g neomycin sulphate, 0.1 g sodium azide, 1 g EDTA and 0.3 % bovine serum albumin in a final volume of 1 l. Plasma samples 100 µl were incubated overnight in a final volume of 600 µl working buffer containing antibody and tracer. Bound and free ligand were separated using dextran coated charcoal. Standard curves were constructed using dog insulin. Intra- and inter-assay coefficients of variation were 6.5 % (N = 30) and 10.1 % (N = 30), respectively. Plasma glucose was measured in triplicate by the glucose oxidase technique with a Technicon AAII autoanalyzer (Tarrytown, NY, USA). The intra-assay coefficient of variation was 1.3 %. Total serum cholesterol and triglycerides were measured by enzymatic methods (Boehringer-Mannheim, FRG). Lipoproteins were quantified according to the Lipid Research Clinic recommendations [20]. Very-low-density, lipoproteins (VLDL) were separated by ultracentrifugation (Airfuge). In the infranatant, cholesterol was measured (LDL + HDL) and LDL precipitated by phosphotungstate (Mg^{2+}) [21]. HDL-cholesterol was then measured in the supernatant. LDL-cholesterol was calculated as the difference between the two measurements. ACE-activity was measured by the radioenzymatic method of Ryan, using a synthetic Hip-Gly-Gly substrate (Ventrex-Kit, Portland, Maine) [22].

Data analysis and statistics

Using the program MINMOD (copyright R. N. Bergman, 1986), the insulin sensitivity index was calculated from FSIGT results. The program accepts as input the temporal pattern of plasma insulin during the modified FSIGT, and the pattern fits a simple (minimal) model of insulin-dependent glucose utilization to the measured glucose pattern. The model is the simplest mathematical representation that can account for the glucose dynamics during the modified FSIGT. The equations of the model are as follows [18]: $dG(t)/dt = -[p_1 + X(t)] \cdot G(t) + p_1 \cdot G_b$, $dX(t)/dt = -p_2 \cdot X(t) + p_3 \cdot I(t)$, where G(t) and I(t) are the plasma glucose and insulin concentrations at every time point (t) following the glucose injection, corresponding to the times when a blood sample is taken. X(t) is a value proportional

Table 1. Clinical and Biochemical Variables in Normal Subjects after a Run-in Placebo Phase and after Double-blind Administration of Placebo (P) or Fosinopril (F) for 3 Weeks. $N = 12$ in each group. Mean with (SEM)

	Treatment Group	Run-in Placebo Phase	Double-blind Phase
Body Weight, kg	P	71 (3)	71 (3)
	F	72 (2)	72 (2)
Body Mass Index, $kg \cdot m^{-2}$	P	22.4 (0.6)	22.5 (0.6)
	F	22.7 (0.4)	22.9 (0.4)
Mean Blood Pressure, mm Hg, Supine	P	92 (3)	91 (4)
	F	90 (2)	83 (2)
Upright	P	97 (2)	96 (2)[a]
	F	90 (4)	87 (2)[a]
Plasma ACE activity, $nmol \cdot ml^{-1} \cdot min^{-1}$	P	92 (8)	87 (7)[b]
	F	106 (6)	24 (8)**,[b]
Potassium, $mmol \cdot l^{-1}$	P	3.9 (0.1)	3.9 (0.1)
	F	3.7 (0.1)	3.9 (0.1)*
Urinary Sodium, mmol per 24 h	P	143 (13)	140 (13)
	F	140 (16)	145 (12)

* $P < 0.05$, ** $P < 0.001$, vs run-in placebo phase by Wilcoxon Test.
[a] $P < 0.05$, [b] $P < 0.001$, vs placebo group by Mann Whitney U-Test

to the insulin concentration above base-line in the remote insulin compartment at every time point (t) following the glucose injection. Thus, it represents the time dependent effect of the dynamic insulin response in accelerating the decline in glucose during the modified FSIGT. G_b is the preinjection glucose concentration. Parameters of the model are estimated by least-squares fitting of the glucose data; p_1 represents the insulin independent glucose removal, and the insulin sensitivity index S_I is calculated as the ratio of two of the fitted model parameters (p_3/p_2).

The disappearance rate of glucose in the first 90 min after glucose injection was expressed as $k = 100*\log 2/t_{1/2}$: $t_{1/2}$ is the time (min) required to halve to glucose concentration, as reported by Ikkos [23]. In this approach, perturbation due to tolbutamide was so slight that a straight line fitted by a logarithmic procedure allowed meaningful estimation of the k-value. The areas under the curves for glucose and insulin during the FSIGT were calculated as the deviations from the baseline over the sampling time.

Statistical analysis was performed with the help of the Statistical Analysis System software package (Version 6.03, SAS Institute, Inc., Cary, NC) and Statview ™ II (Version 1.03). The Mann-Whitney U-test was used for the intergroup comparisons and the Wilcoxon test for intragroup comparisons. $P < 0.05$ was considered significant. Assessment of simple relationships between variables was made by Spearman rank correlation analysis.

Results

Clinical and certain biochemical variables

After the run-in placebo phase, 12 subjects were randomly assigned to continue to take placebo and 12 to take fosinopril. The two groups did not differ significantly in age [mean (SEM) 25 (1) vs 26 (1) y, placebo vs fosinopril group], body weight, body mass index, blood pressure, plasma ACE activity and potassium levels, or 24 h urinary sodium excretion at the end of the run-in placebo phase (Table 1). Plasma sodium [142 (0.3) vs 141 (0.3) mmol·l^{-1}], creatinine [96 (2) vs 99 (2) μmol·l^{-1}] and heart rate [supine, 68 (2) vs 63 (3) beats·min^{-1}] also were similar. The subsequent administration of fosinopril but not of placebo lowered plasma ACE activity ($P < 0.001$), increased plasma potassium ($P < 0.05$) and decreased upright systolic blood pressure [–14 (3) and 0 (3) mmHg after fosinopril and placebo, respectively; $P < 0.01$]. Mean blood pressure was lower in the fosinopril-treated than in the placebo-treated group ($P < 0.01$). Body weight, body mass index, supine and upright heart rate, plasma creatinine [95 (3) vs 94 (2) μmol·l^{-1}] and 24 h urinary sodium did not change after administration either of fosinopril or placebo.

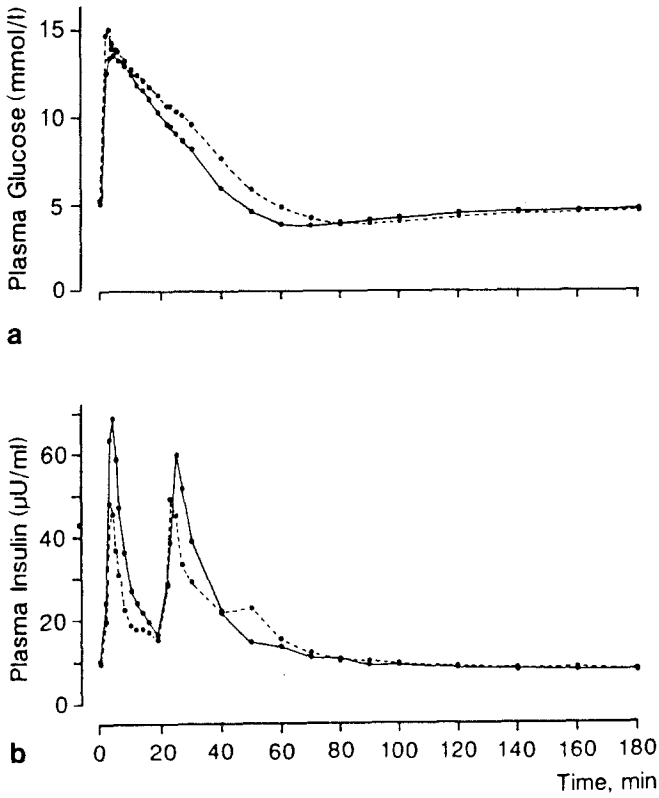

Fig. 1a,b. Mean plasma glucose (**a**) and insulin (**b**) levels during FSIGT procedures after a run-in placebo phase (.....) and after additional 3 weeks of placebo administration (——) in 12 healthy, young, lean men

Table 2. Carbohydrate Indices in Normal Subjects after a Run-in Placebo Phase and after Double-blind Administration of Placebo (P) or Fosinopril (F) for 3 Weeks. $N = 12$ in each group. Mean with (SEM)

	Treatment Group	Run-in Placebo Phase	Double-blind Phase
Fasting Plasma Glucose, mmol·l^{-1}	P	5.0 (0.1)	5.0 (0.1)
	F	5.2 (0.1)	5.1 (0.1)
Insulin, μU·ml^{-1}	P	9.8 (0.8)	9.0 (1.2)
	F	9.7 (0.6)	8.7 (0.5)
Insulin Sensitivity $10^{-4} \times min^{-1}$ ·μU·ml^{-1}	P	12.0 (1.9)	11.5 (1.5)
	F	10.2 (1.2)	12.0 (1.4)
Insulin Independent Glucose Removal, min^{-1}	P	0.020 (0.002)	0.018 (0.002)
	F	0.016 (0.001)	0.018 (0.001)
Area Under the Curve Glucose, mol·l^{-1} ·180 min	P	1.02 (0.02)	1.03 (0.02)
	F	1.08 (0.01)	1.05 (0.02)
Insulin, U·ml^{-1}·180 min^{-1}	P	2.1 (0.2)	2.2 (0.2)
	F	2.0 (0.1)	2.0 (0.1)
K-value, % · min^{-1}	P	–1.75 (0.08)	–1.79 (0.05)
	F	–1.70 (0.06)	–1.88 (0.06)*

* $P < 0.05$, vs run-in placebo phase by Wilcoxon Test

Indices of carbohydrate metabolism

Carbohydrate indices at the end of the run-in placebo phase were similar in the two groups (Table 2). Compared to the run-in placebo phase, the k-value of the glucose disappearance rate was increased ($P < 0.05$) after 3 weeks on fosinopril but not after continued placebo administration (Table 2). A tendency to slightly improved insulin sensitivity and to greater insulin independent glucose removal

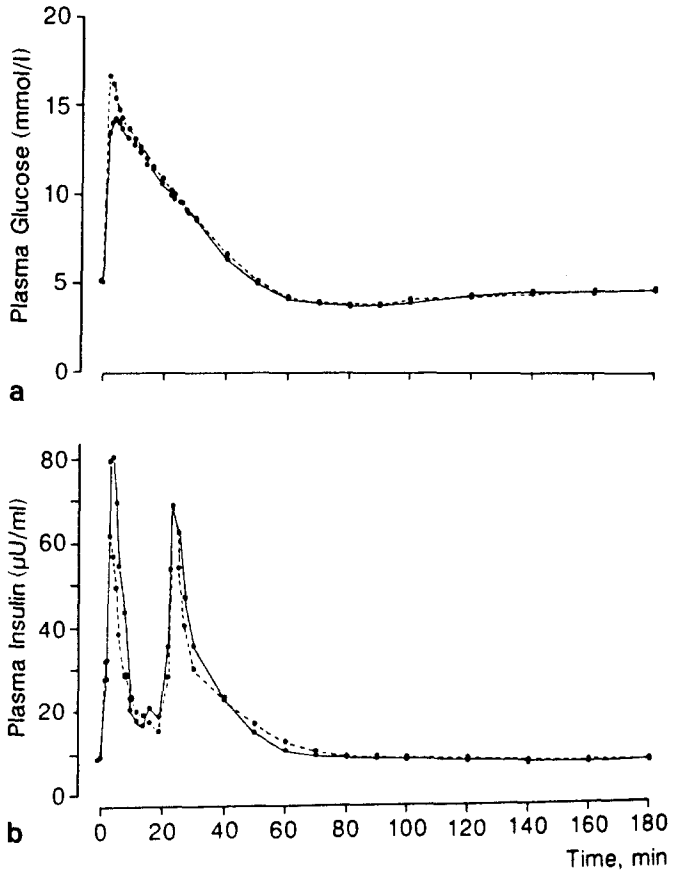

Fig. 2 a, b. Mean plasma glucose (**a**) and insulin levels (**b**) during FSIGT procedures after a run-in placebo phase (.....) and after 3 weeks of ACE-inhibition (——) with fosinopril (20 mg/d × 3 wk) in 12 healthy, young, lean men

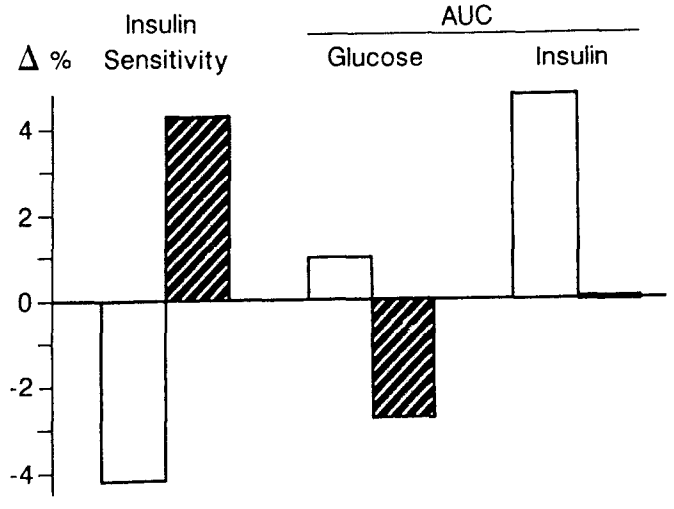

Fig. 3. Percentage changes in insulin sensitivity and areas under the glucose and insulin curves (AUC) after 3 weeks on placebo ($n = 12$) or fosinopril (20 mg/d, $n = 12$). □ Placebo ($n = 12$) ▨ Fosinopril, 20 mg/d (n = 12)

in the group receiving fosinopril did not reach statistical significance (Table 2, Fig. 1–3). Mean fasting plasma insulin and glucose levels did not differ significantly between the fosinopril and placebo-treated groups (Table 2).

Serum lipoproteins

Except for slightly higher serum total ($P < 0.05$) and low density lipoprotein cholesterol (C) ($P < 0.05$) levels at the end of the run-in placebo phase in the group subsequently receiving fosinopril, cholesterol fractions and total triglycerides (Tg) in the two groups were similar before the comparison of fosinopril and placebo. They were not significantly modified after the subsequent 3 week treatment with placebo or fosinopril (Table 3).

The basal serum high density lipoprotein cholesterol (HDL-C) was inversely correlated with total Tg level ($r = -0.44, P < 0.03$).

Subjective tolerance and safety parameters

No symptoms were reported during the administration either of fosinopril or placebo after the placebo phase.

Haemoglobin, haematocrit, white blood cell and platelet counts were not altered after 3 weeks on either fosinopril or placebo.

Discussion

The study has demonstrated that in young healthy men the ACE inhibitor fosinopril, administered in the therapeutic dose of 20 mg daily, hardly affected carbohydrate homoeostasis, and it may even have tended to increase glucose tolerance, as indicated by a slight increase ($P < 0.05$) in the k-value of the plasma glucose disappearance rate after an iv glucose load. Compared to placebo conditions, S_I and insulin-dependent glucose removal also tended to be slightly but not significantly increased during fosinopril treatment, while basal plasma insulin and glucose levels were not changed.

In obese essential hypertensive patients, a slight improvement in insulin sensitivity was noted after 4 months of therapy with captopril [mean dose 81 (24) mg per day]

Table 3. Serum Lipids in Normal Subjects after a Run-in Placebo Phase and after Double-blind Administration of Placebo (P) or Fosinopril (F) for 3 Weeks. $N = 12$ in each group. Mean with (SEM)

	Treatment Group	Run-in Placebo Phase	Double-blind Phase
Cholesterol, mmol·l^{-1}			
Total	P	4.2 (0.2)*	4.3 (0.2)
	F	4.7 (0.2)*	4.6 (0.2)
HDL	P	1.3 (0.1)	1.2 (0.1)
	F	1.2 (0.1)	1.2 (0.1)
LDL	P	2.5 (0.2)*	2.6 (0.2)
	F	3.1 (0.1)*	3.0 (0.1)
VLDL	P	0.4 (0.1)	0.5 (0.1)
	F	0.4 (0.1)	0.4 (0.1)
Total Triglycerides, mmol·l^{-1}	P	1.1 (0.2)	1.1 (0.2)
	F	1.0 (0.1)	1.3 (0.2)

* $P < 0.05$, vs placebo group by Mann Whitney U-Test

[14]. The shorter duration of the present study could theoretically have contributed to the more discrete effects observed with fosinopril. However, this seems unlikely, since captopril, in the high dose of 75–100 mg per day for 10 days itself has been reported to augment insulin sensitivity in a small mixed group of 5 nondiabetic, 1 insulin-dependent and 3 non-insulin-dependent diabetic patients [24] and insulin responsiveness of forearm muscle tissue in some non-insulin-dependent diabetics [25]. On the other hand, insulin sensitivity did not change in 10 insulin-dependent diabetics after administration of 20 mg enalapril daily for 3 months [27]. The discrepant results in these studies [14, 24, 25, 27] could reflect, at least in part, a lack of dietary standardization before testing. Insulin sensitivity may vary depending on the amount and composition of food, which here was standardized for the three days prior to the evaluation.

The potential of ACE-inhibition to influence glucose regulation may depend on the underlying disease, environmental factors, the particular compound and its dose. Moreover, genetic factors, which co-determine the risk of diabetes, essential hypertension and obesity, may also influence insulin sensitivity. Therefore, drug-induced improvement in S_I may be achiveable only in conditions of insulin resistance, as in patients with essential hypertension and obesity [14], but not necessarily in normal humans with basically intact cellular glucose disposal, such as the lean normotensive subjects in the present study. In patients with essential hypertension or either insulin-dependent or non-insulin-dependent diabetes, captopril or enalapril administered in doses 37.5–150 mg or 20–40 mg per day, respectively, also did not notably modify fasting or post-glucose load plasma glucose or insulin values [9, 14]. It follows that various doses of different ACE inhibitors do not seem to adversly affect metabolism, while the clinical relevance of possible discrete regulatory improvement in insulin-mediated glucose disposal during ACE inhibition remains to be clarified.

Several factors should be considered as mechanisms which may promote insulin sensitivity during ACE inhibition: for example, local accumulation of bradykinin [25], decrease of circulating catecholamines [24], potassium sparing [26], or increased access of insulin and glucose to the skeletal muscle tissue induced by the vasodilator action of the ACE inhibitors [14].

Insulin or insulin sensitivity or both modulate the hepatic production and secretion of very-low density lipoprotein, as well as the metabolism of triglyceride-rich lipoproteins by lipoprotein lipase [28, 29]. The production of HDL-C involves the incorporation of remnants of triglyceride-rich lipoproteins [30]. The observed, significant inverse correlation between serum HDL-C and total Tg levels ($P < 0.03$) under defined dietary conditions in healthy lean men is consistent with the latter interaction. On the other hand, fosinopril did not change the serum total lipids or lipoprotein fractions. In patients with essential hypertension, captopril or enalapril are largely neutral with regard to serum cholesterol fractions, but tend slightly to decrease Tg levels [31].

Compliance with drug intake in the present study was acertained by showing distinctly decreased ACE activity in each subject randomized to receive fosinopril, by increased serum potassium and by decreased upright systolic blood pressure in the fosinopril group, and by systematic tablet count. None of the subjects experienced subjective adverse effects and there were no confirmed, clinically significant abnormalities in laboratory test results.

The observed tendency to improved cellular glucose disposal during ACE inhibition with fosinopril in lean young men free from pre-existing abnormalities in carbohydrate and lipoprotein metabolism or blood pressure is a potentially useful characteristic. It deserves further evaluation in individuals at high risk of developing insulin resistance, who are in a age range where other risk factors, possibly interacting with the drug-S_I relationship, may operate, and in patients with impaired insulin sensitivity related to hypertension, obesity, decreased glucose tolerance and diabetes mellitus.

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References

1. Tobey TA, Greenfield M, Kraemer F, Reaven GM (1981) Relationship between insulin resistance, insulin secretion, very low density lipoprotein kinetics and plasma triglyceride levels in normotriglycerydemic man. Metabolism 30: 165–171
2. Stout RW (1970) Development of vascular lesions in insulin-treated animals fed a normal diet. Br Med J 3: 685–687
3. Nakao J, Ito H, Kanayasu T, Murota SI (1985) Stimulatory effect of insulin on aortic smooth muscle cell migration induced by 12-L-hydroxy-5,8,10,14 eicosatetraenoic acid and its modulation by extracellular glucose levels. Diabetes 34: 185–191
4. Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, Shitrit A, Fuchs Z (1985) Hyperinsulinemia. A link between hypertension, obesity and glucose intolerance. J Clin Invest 75: 809–817
5. Weidmann P (1989) Pathogenesis of hypertension accompanying diabetes mellitus. Contrib Nephrol 73: 73–90
6. Reaven GM (1988) Banting lecture 1988: Role of insulin resistance in human disease. Diabetes 37: 1595–1607
7. Houston MC (1989) New insights and new approches 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
8. Williams GH (1988) Converting-enzyme inhibitors in the treatment of hypertension. N Engl J Med 319: 1517–1525
9. Weidmann P, Trost BN, Ferrari P (1989) Treatment of the hypertensive diabetic: focus on calcium channel blockade. In: Zanchetti A, Omae T (eds) How should elderly hypertensive patients be treated? Springer, Berlin Heidelberg New York, pp 85–99
10. Passa P, LeBlanc H, Marre M (1987) Effects of enalapril in insulin-dependent diabetic subjects with mild to moderate uncomplicated hypertension. Diabetes Care 10: 200–204
11. Taguma Y, Kitamoto Y, Futaki G, Ueda H, Monma H, Ishizaki M, Takahasi H, Sekino H, Sasaki Y (1985) Effect of captopril on heavy proteinuria in azotemic diabetics. N Engl J Med 313: 1617–1620
12. Björk S, Nyberg G, Mulec H, Granerus G, Herlitz H, Aurell M (1986) Benefical effects of angiotensin converting enzyme in-

hibition on renal function in patients with diabetic nephropathy. Br Med J 293: 471–474
13. Rett K, Jauch KW, Wicklmayr M, Fink E, Dietze G, Mehnert H (1989) Increased insulin-responsivness by ACE-inhibition in noninsulin dependent diabetes mellitus. Adv Exp Med Biol 247: 207–213
14. Pollare T, Lithell H, Berne C (1989) 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
15. Singhui SM, Duchin KL, Morrison RA, Willard DA, Everett DW, Frantz M (1988) Disposition of fosinopril sodium in healthy subjects. Br J Clin Pharmacol 25: 9–15
16. Nuttall FQ, Gannon MC, Wald JL, Ahmed M (1985) Plasma glucose and insulin profiles in normal subjects ingesting diets of varying carbohydrate, fat, and protein content. J Am Coll Nutr 4: 437–450
17. Beard JC, Bergman RN, Kenneth Ward W, Porte D Jr (1986) The insulin sensitivity index in nondiabetic man. Correlation between clamp derived and IVGTT-derived values. Diabetes 35: 362–369
18. Bergman RN, Prager R, Volund A, Olefsky JM (1987) Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 79: 790–800
19. Yang YJ, Youn JH, Bergman RN (1987) Modified protocols improve insulin sensitivity estimation using the minimal model. Am J Physiol 253: E595–E602
20. Lipid Research Clinics Program (1974) Manual of laboratory operations. Lipid and lipoproteins analysis (publication NIH) 75–628, US Department of Health, Education of Welfare
21. Burstein M, Scholnik HR, Morfin R (1970) Rapid methods for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 11: 583–595
22. Ryan JW, Chung A, Ammons C, Carlton ML (1977) A simple radioassay for angiotensin-converting enzyme. Biochem J 167: 501–504
23. Ikkos D, Luft R (1957) On the intravenous glucose tolerance test. Acta Endocrinol (Copenh) 25: 312–334
24. Ferrière M, Lachkar H, Richard JL, Bringer J, Orsetti A, Mirouze J (1985) Captopril and insulin sensitivity. Ann Intern Med 102: 134–135
25. Rett K, Lotz N, Wicklmayr M, Fink E, Jauch KW, Günther B, Dietze G (1988) Verbesserte Insulinwirkung durch ACE-Hemmung beim Typ-II-Diabetiker. Dtsch Med Wochenschr 113: 243–249
26. Helderman JH, Elahi D, Andersen DK, Raizes GS, Tobin JD, Shocken D, Andres R (1983) Prevention of glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 32: 106–111
27. Leblanc H, Thote A, Billault B, Porquet D, Fisch A, Passa P (1988) Absence d'effet de l'enalapril sur le contrôle glycémique et la sensibilité périphérique à l'insuline chez 10 diabétiques insulino-dépendants traités par infusion continue sous-cutanée d'insuline. Presse Méd 17: 2277–2280
28. Abrams JJ, Ginsberg H, Grundy SM (1982) Metabolism of cholesterol and plasma triglicerides in nonketotic diabetes mellitus. Diabetes 31: 903–910
29. Taskinen MR, Kuusi T, Helve E, Nikkilä EA, Yki-Järvinen H (1988) Insulin therapy induces antiatherogenic changes of serum lipoproteins in noninsulin-dependent diabetes. Arteriosclerosis 8: 168–177
30. Schaeffer EJ, Levy RI (1985) Pathogenesis and management of lipoprotein disorders. N Engl J Med 312: 1300–1310
31. Rosman J, Weidmann P, Ferrari P (1990) Antihypertensive drugs and serum lipoproteins. J Drug Dev 3 [Suppl 1]: 129–139

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