

# Comparison of effects of quinapril and metoprolol on glycaemic control, serum lipids, blood pressure, albuminuria and quality of life in non-insulin-dependent diabetes mellitus patients with hypertension

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**Abstract.** Östman J, Asplund K, Bystedt T, Dahlöf B, Jern S, Kjellström T, Lithell H (Huddinge University Hospital, Karolinska Institute, Stockholm, Regional Hospital, Umeå, Karolinska Hospital, Stockholm, SU/Östra University Hospital, Gothenburg, Helsingborg Hospital, Helsingborg, University Hospital, Uppsala, Sweden). Comparison of effects of quinapril and metoprolol on glycaemic control, serum lipids, blood pressure, albuminuria and quality of life in non-insulin-dependent diabetes mellitus patients with hypertension. *J Intern Med* 1998; **244**: 95–107.

**Objective.** To compare the long-term effects of the angiotensin-converting enzyme (ACE)-inhibitor quinapril and the cardioselective beta-adrenergic blocking agent metoprolol on glycaemic control, with glycosylated haemoglobin (HbA<sub>1c</sub>) as the principal variable, in non-insulin-dependent diabetes mellitus (NIDDM) patients with hypertension.

**Design.** A randomized, double-blind, double-dummy, multicentre study during 6 months preceded by a 4 week wash-out and a 3 week run-in placebo period. Quinapril (20 mg) and metoprolol (100 mg, conventional tablets) were given once daily. No change was made in the treatment of diabetes (diet and hypoglycaemic agents).

**Subjects.** Seventy-two patients fulfilling the criteria were randomized and entered the double-blind period. Twelve patients did not complete the study. Sixty patients, 26 on quinapril and 34 on metoprolol, were available for the final analysis.

**Main outcome measures.** The effect was assessed by changes in HbA<sub>1c</sub>, the fasting serum glucose and the

post-load serum glucose, C-peptide and insulin levels during the oral glucose tolerance test.

**Results.** In the quinapril group, the fasting serum glucose, oral glucose tolerance and the C-peptide and insulin responses, determined as the incremental area under the curves (AUC), showed no change, but the mean HbA<sub>1c</sub> level increased from  $6.2 \pm 1.1\%$  to  $6.5 \pm 1.3\%$  ( $P < 0.05$ ). In the metoprolol group, the rise in the mean level of HbA<sub>1c</sub>, from  $6.3 \pm 1.0\%$  to  $6.8 \pm 1.3\%$  ( $P < 0.01$ ), tended to be more marked than after quinapril, although there was no significant difference between the increments. The mean fasting serum glucose showed an increase from  $9.1 \pm 1.9$  mm to  $10.1 \pm 2.8$  mm ( $P < 0.01$ ) which correlated significantly with the duration of diabetes ( $P < 0.01$ ) and the increase in fasting serum triglycerides ( $P < 0.001$ ). Moreover, in the metoprolol group we found significant decreases in the oral glucose tolerance as well as C-peptide and insulin responses to the glucose load.

**Conclusions.** Treatment with quinapril for 6 months appears to have advantages over metoprolol in NIDDM patients with hypertension. Although treatment with quinapril or metoprolol over 6 months was concomitant with a rise in the HbA<sub>1c</sub>, increased fasting blood glucose, decreased oral glucose tolerance and decreased C-peptide and insulin responses to a glucose challenge were observed only in patients treated with metoprolol.

**Keywords:** cholesterol, C-peptide, glycosylated haemoglobin (HbA<sub>1c</sub>), insulin, oral glucose tolerance test, triglycerides.

## Introduction

Non-insulin-dependent diabetes mellitus (NIDDM), hypertension and dyslipidaemia, which frequently exist in the same person, are major risk factors in atherosclerotic disorders [1, 2]. For this reason, drugs with no adverse effects on glucose and lipid metabolic control are preferred in the treatment of hypertension in patients having NIDDM [3, 4]. With regard to the clinical relevance, i.e. the course of cardiovascular disorders in NIDDM, the importance of this choice of antihypertensive treatment is still unknown [5]. Moreover, studies on the effects of many antihypertensive drugs on glucose metabolic control in NIDDM have shown conflicting results [6, 7].

Angiotensin-converting enzyme (ACE) inhibitors have been observed to increase the peripheral insulin sensitivity, when estimated by the euglycaemic clamp technique [8–12]. In line with these findings, severe hypoglycaemic episodes have occurred only a few hours or days after starting treatment with an ACE inhibitor [13, 14]. However, a large number of clinical studies, usually uncontrolled, brief and covering few patients [15, 16], have found that ACE treatment had no significant effect on glycaemic control in NIDDM or on insulin and C-peptide levels [17] and only a few have indicated an improvement, with reduction in fasting blood glucose [18] or glycosylated haemoglobin (HbA<sub>1c</sub>) [19, 20].

The findings concerning the effects of beta-adrenergic blocking agents on glucose metabolism in NIDDM are equally conflicting. However, in most clinical studies, a deterioration in glucose tolerance has occurred after non-cardioselective adrenergic blocking agents [21–23], but not after cardioselective agents [21–24], some have shown a worsening also after these [25] and one [26] has shown an improvement with both types.

In view of all this, it seemed pertinent to compare the long-term effects of one ACE-inhibitor, quinapril, which is a new drug, and one cardioselective beta-adrenergic blocking agent, metoprolol, on the glycaemic control in a large group of patients with NIDDM and hypertension. The principal parameter chosen was HbA<sub>1c</sub>. Fasting serum glucose, oral glucose tolerance and C-peptide and insulin responses to oral glucose load were also monitored. Moreover, the effects on serum lipids, urinary excretion of albumin and quality of life were investigated.

## Research design and methods

### *Patients*

Patients who had had NIDDM in stable blood glucose control for at least 2 months (treated with diet alone or with oral hypoglycaemic drugs) and essential hypertension, or drug-treated or about to be put on drug treatment, and who were between 35 and 75 years of age, were considered for participation in this study. To be eligible to enter the run-in wash-out period, the patients had to meet the study criteria of having a supine diastolic blood pressure of 95–109 Hg (Korotkoff phase V), a serum glucose level of 6–9 mM in patients on diet alone and 6–11 mM in patients on oral antidiabetic drugs and a body mass index <35 kg m<sup>-2</sup>. Other exclusion criteria were: congestive heart failure, myocardial infarction, angina pectoris treated with drugs other than nitrates, haemodynamically serious valvular heart disease and secondary or malignant hypertension. Treatment with thiazides and/or lipid-lowering agents in the preceding 12 month period disqualified the patient, as did treatment with loop-diuretics in the preceding 3 month period and concomitant chronic therapy with non-steroidal anti-inflammatory drugs. Serum levels of AST or ALT of >2 µcat L<sup>-1</sup>, hyperlipoproteinaemia, defined as cholesterol >8 mM, triglycerides >4 mM and proteinuria (>0.5 g L<sup>-1</sup>) were also exclusion criteria. Therapy with antidiabetic drugs continued to be given throughout the study in the same dose as at randomization. If the diastolic blood pressure could not be maintained at 90 mmHg during the double-blind period, additional treatment with felodipine was permitted, since it has been shown to lower blood pressure without significantly impairing glucose tolerance in patients with NIDDM [27]. In order to detect a 0.3% difference with 5% significance and 80% power in the HbA<sub>1c</sub> level (the principal variable) between the two groups, assuming a normal distribution, 64 patients would be needed in the final evaluation. This was based on the finding of 0.42% SD in the literature [26].

### *Study design*

After a 4 week wash-out period, the patients started placebo treatment, and underwent a 3 week quality of life assessment. After this 7 week period, the patients were randomized either to single-dose treatment with quinapril, 20 mg daily, or to treatment

with metoprolol, 100 mg (conventional tablets) daily in a double-blind, double-dummy fashion. The doses were chosen to give equipotency in the antihypertensive effect. Each patient found eligible to enter the run-in period was given a patient number for a series unique for each in the 15 participating centres. The study was performed in accordance with the Declaration of Helsinki, Tokyo Revision. The protocol was reviewed and approved by the Ethics Committee at the Karolinska Institute, Stockholm, Sweden, the regional ethics committees and the Swedish Medical Products Agency.

### *Procedures*

Measurements of blood pressure and heart rate were generally made by the same person at about the same time in the mornings, before drug intake. The patients were instructed to avoid undue physical activity and refrain from coffee and smoking before the measurements. Blood pressure was measured in the supine position following 5 min of rest and standing after 1 min. All measurements were made on the right arm and with a sphygmomanometer, standard or cone shaped. The mean of two measurements, read at the nearest 2 mmHg, was recorded. The heart rate was measured by counting the radial pulse during 15 s or, if arrhythmia was present, for 1 min, first in the supine position as above, then standing. Blood pressure and heart rate measurements were performed during the run-in period before the quality of life assessment started, at the point of randomization, and after 6 weeks, 3 and 6 months (end) in the double-blind period. Body-mass index (BMI) was calculated as body weight (kg) / height<sup>2</sup> (m).

Glycosylated haemoglobin was estimated in samples collected at randomization, and after 3 and 6 months in the double-blind period. Fasting blood samples for analyses of serum glucose were collected at randomization and again after 2 weeks, 3 and 6 months. The patient was asked about hypoglycaemic symptoms throughout the whole study. An oral glucose tolerance test (OGTT) was performed at the time of randomization, i.e. before the start of active drug treatment, and after the 6-month double-blind period. The OGTT was performed in the morning after an overnight (10 h) fast; no drug intake was allowed. After a baseline sample had been taken, the patient ingested 75 g of glucose and additional blood samples were taken for analyses of glucose, C-peptide and

insulin in serum at 30, 60, 90, 120, 150 and 180 min. The net (incremental) areas under the curve (AUC) were calculated by the trapezoidal rule. Fasting samples for the estimate of cholesterol, HDL cholesterol and triglycerides in serum were collected at randomization and after 3 and 6 months in the double-blind period. LDL was calculated by the Friedewald formula [28]. Serum lipoprotein-(a) was estimated in samples collected at randomization and after 6 months in the double-blind period. Albuminuria was investigated during the night and was calculated as the milligrams of albumin excreted during 12 h. On the day before urine collection, the patients were instructed to avoid physical exertion. Liver and kidney functions were followed throughout the study, and blood haematology was performed before inclusion, at the time of randomization and at the end of the study.

### *Analytical procedures*

All analytical procedures were performed at CALAB, Clinical Trial Centre, Stockholm, Sweden. Serum insulin was measured with an automatic immunoassay system, cross-reactivity with pro-insulin was 40% and the total coefficient of variation <7%. Serum C-peptide was measured with radioimmunoassay; cross reactivity with proinsulin was <20% and the intra- and interassay coefficients of variation were 3 and 8%, respectively. HbA<sub>1c</sub> was analysed in capillary blood by ion-exchange (fast protein) chromatography with intra- and interassay coefficients of variation <1%. Cholesterol and triglycerides in serum were analysed enzymatically. Serum HDL cholesterol was measured after the precipitation of LDL and VLDL from the sample. Serum lipoprotein (a) and urinary albumin were analysed by photometric immunoturbidimetric tests.

### *Quality of life*

Quality of life was assessed regularly during the study on a self-administered 40-item 'assessment of symptoms and psychological effects in cardiovascular therapy' (ASPECT) scale [29, 30]. Assessments were performed twice a week during 3 weeks of placebo treatment and during 3 weeks at the beginning and end of the 6 month active treatment period. The data reported here represent changes from baseline to the final treatment period.

### Statistical analysis

Results are expressed as means  $\pm$  standard deviation (SD) or standard error (SE). Values for urinary albumin excretion were logarithmically transformed before analysis, because of the positively skewed distributions, and the geometric mean with 95% confidence intervals are given.

The Cochran–Mantel–Haenzel test was used to evaluate the effects of the main treatment by comparing blood pressure, heart rate and metabolic variables. This method, based on so-called ridit scores, corresponds essentially to a Wilcoxon rank sum test, but it takes the multicentre aspect into account.

In the analysis of the quality of life data, 95% confidence intervals for the mean changes in within-group ratings, based on Student's *t*-test distribution, were calculated from the baseline to the early and late treatment periods. Comparisons between the study groups were performed by analysis of variance (ANOVA).

## Results

### Patients

Altogether 134 patients were asked to participate in the study. After the wash-out period, 87 patients were eligible for the run-in 3 week quality of life assessment. At the time of randomization, 15 patients did not fulfil the criteria for continuing the double-blind period: nine in the quinapril group and six in the metoprolol group. Another patient in the metoprolol group was omitted because of amaurosis fugax. A few patients who did not fulfil the study criteria, but were randomized by mistake, have later been excluded. During the double-blind period, five more patients in the quinapril group were excluded: one patient with a hip fracture was found dead at home, one patient had a suspected myocardial infarction, one had cardiac failure, one dropped out after 4 months because of a cough and one after a month because of persistent stomach pain from the time of randomization. At the end of the study, four patients were omitted from the final evaluation. Three of these patients belonged to the metoprolol group and were omitted because of treatment with diuretics or beta-blockers during the study or because active treatment was stopped 1 month too early. This was also the case with the quinapril-treated patient. Thus, 60 patients remained for the final analysis: 26 in the quinapril group and 34 in the metoprolol group.

**Table 1** Characteristics of patients at baseline during the placebo period

	Quinapril ( <i>n</i> = 26)	Metoprolol ( <i>n</i> = 34)
Sex, men/women (%)	18/8 (69/31)	19/15 (56/44)
Age (years)	65 $\pm$ 6	64 $\pm$ 8
Body-mass index (kg m <sup>-2</sup> )	28.6 $\pm$ 3.2	28.6 $\pm$ 3.4
Median duration of diabetes (years)	4.6	3.7
On treatment with oral antidiabetic agents (%)	54	56
SU/BG/SU + BG ( <i>n</i> )	10/0/4	14/1/4
Median duration of treated hypertension (years)	11.7	8.8
On previous treatment with antihypertensive agents (%)	77	71
Regular smokers (%)	18	18

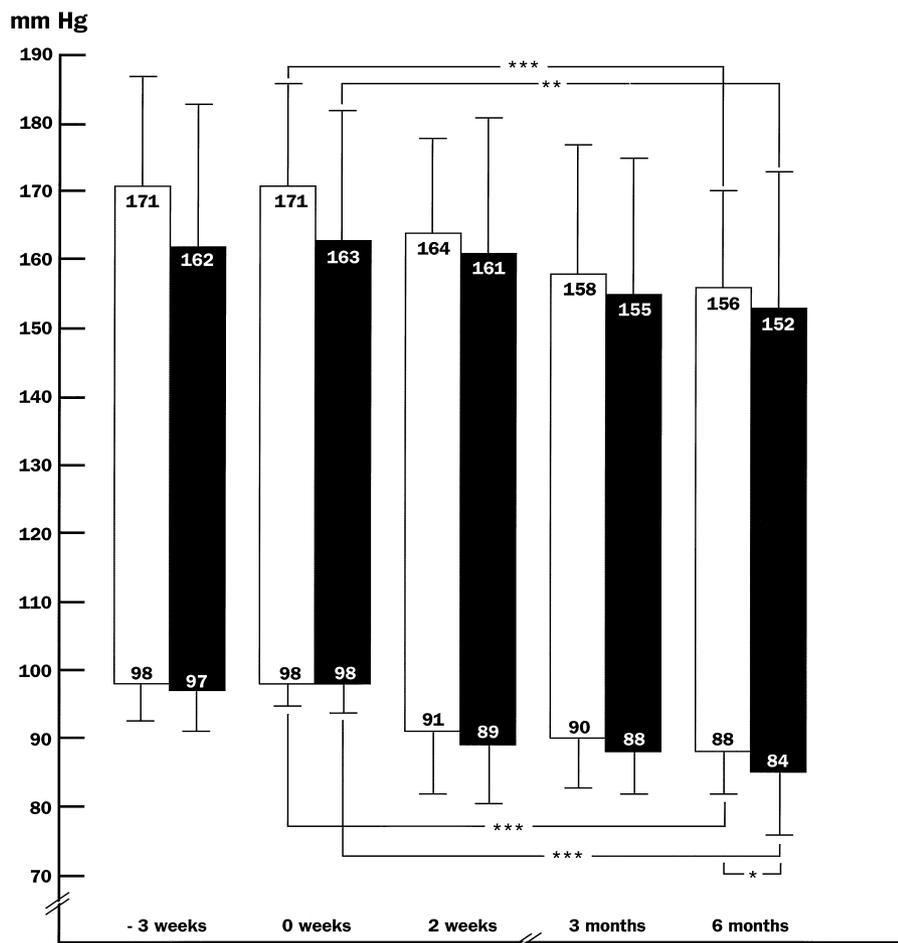
Values are given as means  $\pm$  SD, if not otherwise indicated. SU, sulphonylurea; BG, biguanides.

### Comparability of the two groups at baseline

Quinapril-treated and metoprolol-treated patients were of the same age, but there was a male predominance amongst quinapril-treated patients (Table 1). The median duration of diabetes was slightly, but not significantly, longer in the quinapril group, but the two groups had the same median duration of treated hypertension. The percentage who had been on treatment with ACE inhibitors, alone or in combination with other antihypertensive drugs, was higher in the quinapril-treated than in the metoprolol-treated group (27 vs. 12%). Otherwise there were no differences between the two study groups.

### Blood pressure and heart rate

The two study drugs significantly reduced the systolic and diastolic blood pressures, which did not differ at baseline (Fig. 1). The reduction in supine diastolic pressure was more pronounced (*P* < 0.05) after metoprolol treatment. No differences between the reductions in standing systolic and diastolic blood pressures were found. A supine diastolic blood pressure of <90 mmHg or a fall of at least 10 mmHg was obtained in 20 patients (77%) in the quinapril group and 29 (85%) in the metoprolol group. The heart rate decreased in the metoprolol group but at 6



**Fig. 1** Supine systolic and diastolic blood pressures (mean  $\pm$  SD) at 3 weeks prior to the double-blind period, at baseline and at 2 weeks, 3 months and 6 months after treatment with  $\square$ , quinapril and  $\blacksquare$ , metoprolol, respectively. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

months the decrease was not significant. This finding was ascribed to a marked rise in the heart rate of some patients, mainly females. This could be due to a certain non-compliance in those given metoprolol. Although there is no direct relationship between the beta-blockade and the antihypertensive effect, it is possible that the antihypertensive effect of metoprolol in our study was more marked over 24 h than found in the mornings.

*Glycaemic control*

A slight increase in the HbA<sub>1c</sub> level was seen in both study groups: in the quinapril group from  $6.2 \pm 1.1\%$  to  $6.5 \pm 1.3\%$  ( $P < 0.05$ ) and in the metoprolol group from  $6.3 \pm 1.0\%$  to  $6.8 \pm 1.3\%$  ( $P < 0.01$ ) at 6 months (Fig. 2). The difference at 6 months between the study groups was not significant. In the 12 patients who had had diabetes for more than 5 years, the HbA<sub>1c</sub> levels in the quinapril group showed

the same increase as the patient material as a whole, but in the metoprolol group ( $n = 12$ ) the increase was more marked, 1.1% higher than in the whole group. There was a significant correlation between the duration of diabetes and the increase in HbA<sub>1c</sub> level ( $r = 0.48$ ;  $P < 0.01$ ) in the metoprolol group, but no correlation was observed in the quinapril group. There were no changes in the mean fasting serum glucose level (Fig. 3) in the patients treated with quinapril, but in those on metoprolol it increased gradually from  $9.1 \pm 1.9$  mM at baseline, to  $10.1 \pm 2.8$  mM ( $P < 0.001$ ) at 6 months. Although special attention was paid to recording hypoglycaemic episodes, none was observed in any of the study groups.

Figures 4 and 5 show findings concerning the OGTT before and after 6 months of antihypertensive treatment. At baseline, there were no differences between the study groups as regards the mean fasting serum levels of glucose, C-peptide and insulin

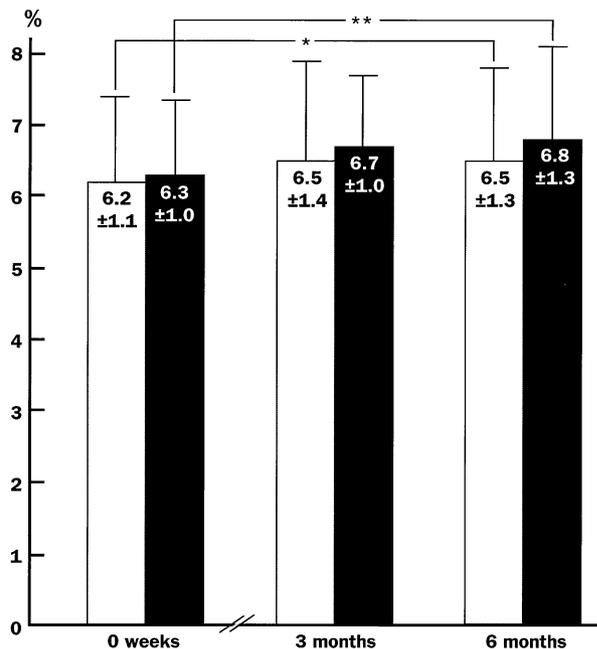


Fig. 2 Glycosylated haemoglobin (HbA<sub>1c</sub>) (mean ± SD) at baseline and after 3 and 6 months' treatment with □, quinapril and ■, metoprolol, respectively. \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .

(not charted). Likewise, the incremental AUC of glucose and C-peptide did not differ. After 6 months, no changes in the oral glucose tolerance and serum C-peptide levels were seen in the quinapril group. In those on metoprolol, the oral glucose tolerance decreased and the mean serum glucose levels were significantly higher at 60 ( $P < 0.05$ ), 90 ( $P < 0.01$ ), 120, 150 and 180 min ( $P < 0.01$ ). The mean serum glucose levels at 6 months were significantly ( $P < 0.05$ ) higher than those of the quinapril-treated patients at fasting, 30 and 150 min. The glucose AUC was unchanged in both study groups. The C-peptide AUC decreased ( $P < 0.05$ ) only in the metoprolol group and the C-peptide levels were significantly lower at 90 ( $P < 0.01$ ), 120 ( $P < 0.01$ ), 150 and 180 min ( $P < 0.05$ ) at 6 months, as compared to baseline. Similarly, the insulin AUC decreased only in the metoprolol group – from  $27.1 \pm 3.6$  nM min (mean ± SE) to  $24.2 \pm 4.3$  nM min ( $P < 0.05$ ), but remained unchanged ( $30.5 \pm 3.9$  vs.  $28.7 \pm 4.5$  nM min) in the quinapril group (data not charted).

#### Body weight

The quinapril group showed a slight but significant ( $P < 0.01$ ) decrease in the mean body weight from  $84.7 \pm 12.1$  kg to  $83.2 \pm 12.3$  kg. In contrast, the

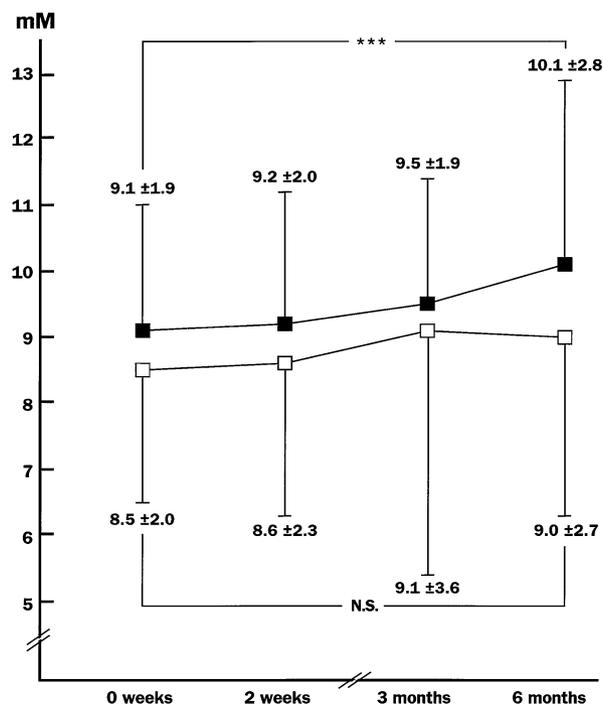


Fig. 3 Fasting serum glucose concentrations (mean ± SD) at baseline and at 2 weeks, 3 months and 6 months after treatment with □, quinapril and ■, metoprolol, respectively. \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .

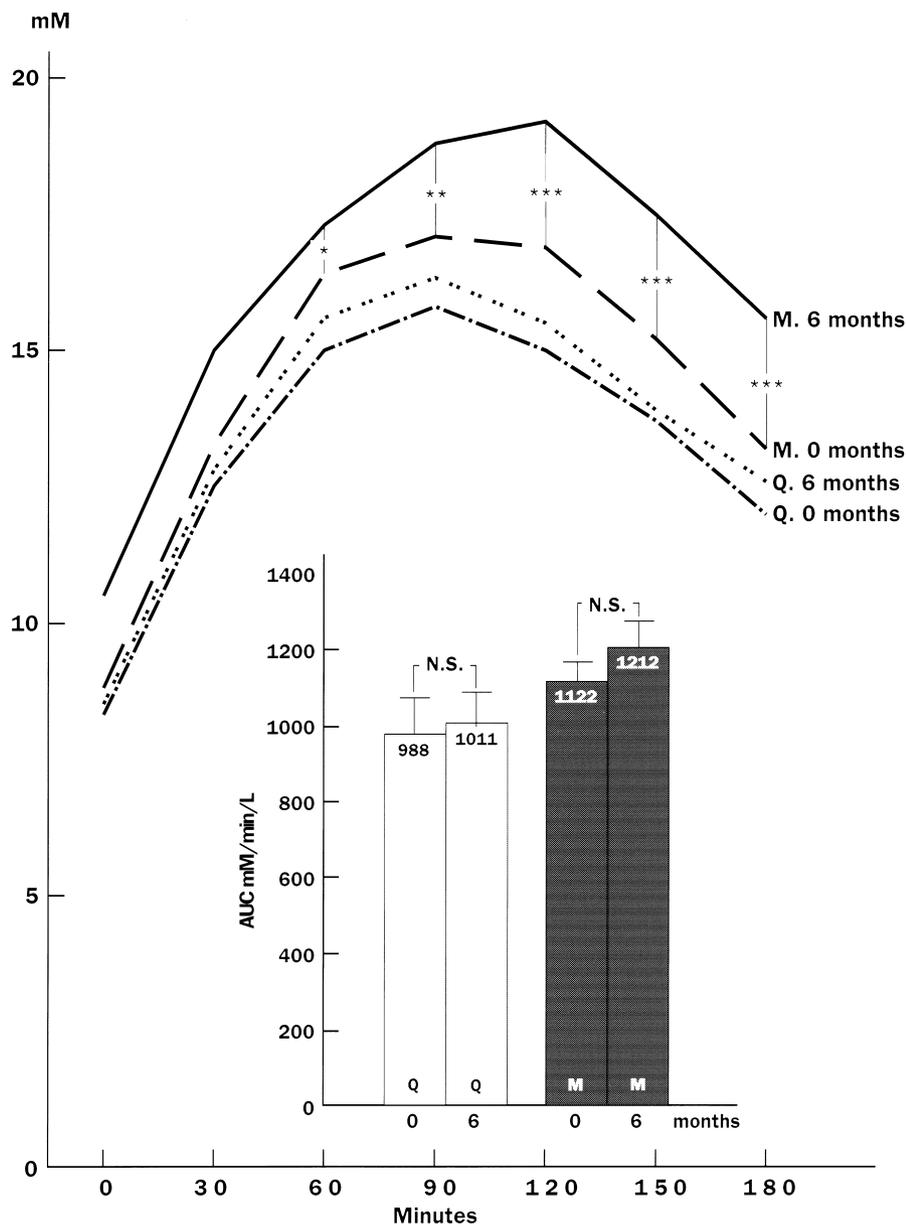
mean body weight in metoprolol-treated patients remained unchanged,  $83.6 \pm 13.6$  kg at baseline and  $84.1 \pm 13.7$  at 6 months, the difference between the groups being significant ( $P < 0.001$ ).

#### Lipids

Increased serum triglyceride levels ( $>2.3$  mM) were found in about 30% of the patients. The mean serum triglyceride level was unchanged in the quinapril-treated patients, but it increased significantly in those on metoprolol, from  $1.9 \pm 1.2$  to  $2.2 \pm 1.5$  mM ( $P < 0.05$ ). In the metoprolol group, the changes in triglyceride levels correlated with the changes in HbA<sub>1c</sub> ( $r = 0.59$ ,  $P < 0.001$ ). The basal levels of the mean total serum cholesterol were similar (mean 5.8 mM) in the treatment groups during the study, as also were the levels of serum HDL (1.3 mM). The mean serum levels of LDL (3.7 mM) and lipoprotein-(a) ( $0.2$  g L<sup>-1</sup>) were not affected in either group.

#### Albuminuria

Microalbuminuria, defined as a urinary albumin excretion of 15–150 mg per 12 h, was observed at



**Fig. 4** Serum glucose concentrations (mean  $\pm$  SE) during an oral glucose tolerance test at baseline and after 6 months' treatment with  $\square$ , quinapril and  $\blacksquare$ , metoprolol, respectively. The net (incremental) area under the curve (AUC) was calculated by the trapezoidal rule. \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .

baseline in 12 patients, of whom four were later treated with quinapril and eight with metoprolol. This prevalence of albuminuric alterations agrees with several reports on NIDDM. Macroalbuminuria ( $>150$  mg per 12 h) was seen in six patients, three of whom were later treated with quinapril and three with metoprolol. The urinary albumin excretion was unchanged in both study groups, being in the quinapril-treated patients 5.5 mg per 12 h (1.9–15.5) (geometric mean with approximately 95% CI) at baseline and 4.6 (1.3–15.8) mg per 12 h at 3 months and 3.5 (1.0–11.7) mg per 12 h at 6

months. The corresponding values in the metoprolol group were 7.4 (3–14.5), 3.6 (1.3–9.6) and 4.0 (1.6–10.4) mg per 12 h, respectively.

*Quality of life*

There were no differences in wellbeing indices or subjective symptom scores between the two groups at baseline (Table 2). No significant intergroup differences were observed in any of the quality of life variables during the early follow-up period. Global wellbeing and the total symptom scores did not

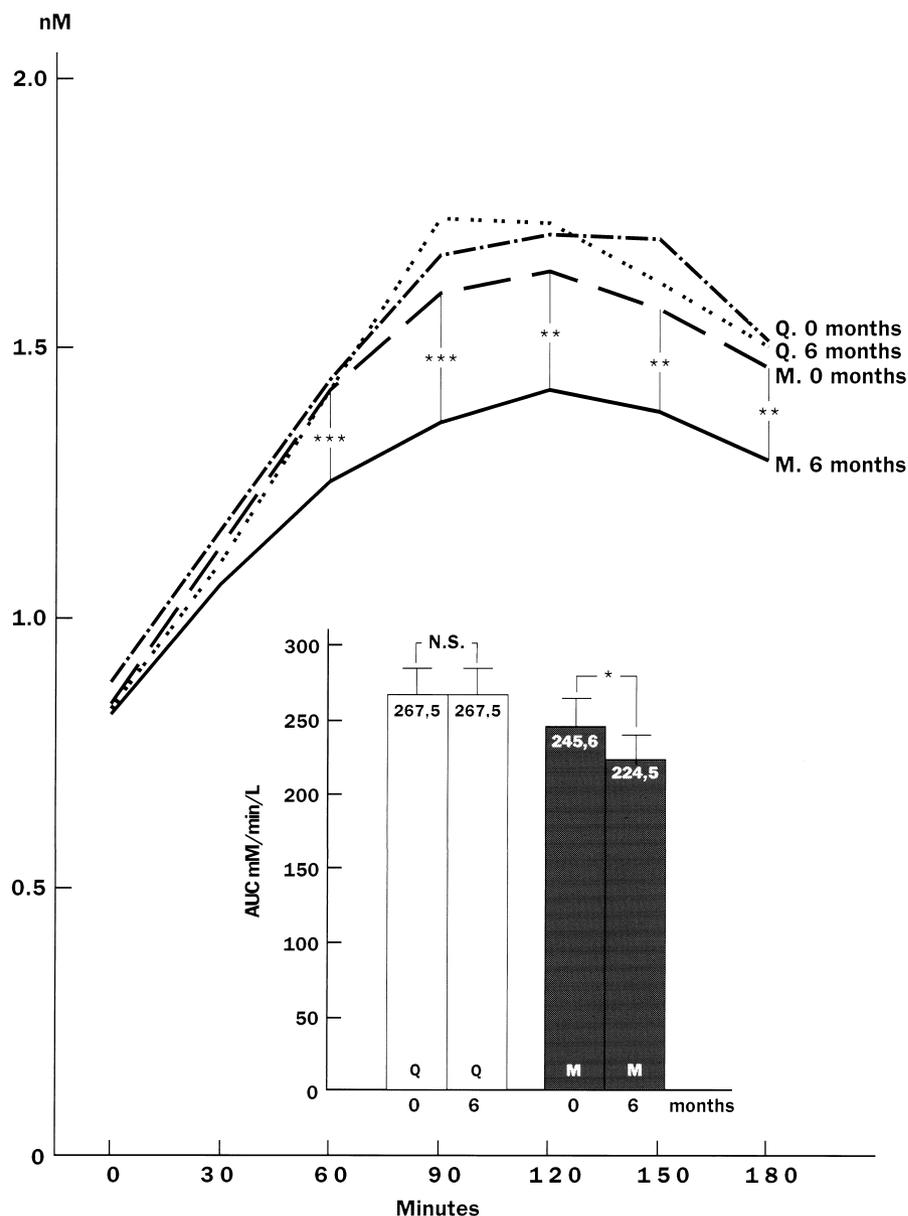


Fig. 5 Serum C-peptide concentrations (mean  $\pm$  SE) during the oral glucose tolerance test shown in Fig. 4. \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .

change during treatment with quinapril or metoprolol. The complaint about cold digits increased in the metoprolol group (M) and decreased in the quinapril group (Q) (M vs. Q,  $P < 0.01$ ). A similar pattern was observed for muscular weakness (M vs. Q,  $P < 0.05$ ). Symptoms of sweating and alterations in taste perception increased in the metoprolol group (M vs. Q,  $P < 0.05$  and  $P < 0.05$ , respectively). Cough increased in the quinapril group (M vs. Q,  $P < 0.01$ ). Although, fatigue, headache and nervousness decreased ( $P < 0.05$ ) during quinapril treatment, there were no intergroup differences.

## Discussion

Treatment with metoprolol was associated with impaired glycaemic control, as demonstrated by a gradual increase in the mean serum glucose concentration, increase in the mean HbA<sub>1c</sub> level by 0.5% and a decrease in oral glucose tolerance. In the quinapril group, only an increase (0.3%) in the HbA<sub>1c</sub> level was observed, which tended to be smaller, although not significantly so. No changes in the antidiabetic treatment, i.e. neither the doses of the drugs nor the diet, were made, according to the study protocol. Since

**Table 2** Quality of life during long-term treatment with quinapril and metoprolol

	Quinapril (n = 26)	Metoprolol (n = 34)	Significance M vs. Q
<i>Summary of wellbeing and subjective symptom scores</i>			
<i>Global wellbeing</i>			
Baseline	75.93 (2.82)	72.78 (3.38)	
Δ Baseline 5/6 months	+3.27 (2.03)	+0.66 (2.25)	NS
<i>Total symptom scores</i>			
Baseline	11.44 (1.31)	13.84 (1.70)	
Δ Baseline 5/6 months	-1.13 (0.82)	+0.75 (1.05)	NS
<i>Prevalence of symptoms</i>			
<i>Cold digits</i>			
Baseline	12.25 (2.96)	9.68 (2.36)	
Δ Baseline 5/6 months	-2.69 (1.52) ( <i>P</i> < 0.05)	+5.13 (1.88) ( <i>P</i> < 0.01)	<i>P</i> < 0.01
<i>Muscular weakness</i>			
Baseline	12.62 (2.27)	14.56 (3.29)	
Δ Baseline 5/6 months	-2.39 (2.07)	+3.47 (1.65) ( <i>P</i> < 0.05)	<i>P</i> > 0.05
<i>Sweating</i>			
Baseline	10.92 (2.96)	12.37 (4.18)	
Δ Baseline 5/6 months	-0.57 (1.89)	+11.30 (4.36) ( <i>P</i> < 0.05)	<i>P</i> < 0.05
<i>Taste disturbances</i>			
Baseline	6.34 (0.86)	4.94 (0.73)	
Δ Baseline 5/6 months	-0.10 (0.42)	+3.09 (1.14) ( <i>P</i> < 0.05)	<i>P</i> < 0.05
<i>Cough</i>			
Baseline	7.39 (1.47)	11.84 (2.88)	
Δ Baseline 5/6 months	+9.97 (4.24) ( <i>P</i> < 0.05)	-1.86 (1.75)	<i>P</i> < 0.01
<i>Fatigue</i>			
Baseline	20.50 (3.92)	27.54 (4.60)	
Δ Baseline 5/6 months	-8.06 (3.73) ( <i>P</i> < 0.05)	-3.20 (2.52)	NS
<i>Headache</i>			
Baseline	11.58 (2.29)	17.89 (3.58)	
Δ Baseline 5/6 months	-3.09 (1.43) ( <i>P</i> < 0.05)	-3.35 (2.95)	NS
<i>Nervousness</i>			
Baseline	10.19 (1.74)	13.99 (3.58)	
Δ Baseline 5/6 months	-2.17 (0.93) ( <i>P</i> < 0.05)	-3.01 (3.50)	NS

M, metoprolol; Q, quinapril.

none of the metabolic characteristics at baseline differed significantly between the two study groups, the changes during the double-blind period were essentially related to the type of antihypertensive treatment. The more pronounced blood-pressure lowering effect (supine diastolic blood pressure) in the metoprolol-treated group indicates that the doses were not fully equipotent. Although the body weight of the study groups changed in opposite directions, in agreement with previous studies, this presumably had a minor impact on the metabolic control of glu-

cose. The 6 month changes in fasting blood glucose and body weight showed no correlation in either of the two study groups. It is of interest to note that the rates of increase in the fasting levels of the serum glucose and the HbA<sub>1c</sub> were of the same size as those observed in the obese NIDDM patients treated with oral hypoglycaemic drugs during the second and third years, in the large United Kingdom Prospective Diabetes Study [31], which suggests that the deterioration in glucose metabolic control to some extent was related to the natural course of diabetes.

More recently published studies [32–34] have shown that ACE treatment has no effect on glycaemic control. In a recent placebo-controlled study in 17 patients with NIDDM, captopril reduced the production of hepatic glucose and increased the disposal of glucose, which indicates an increased insulin sensitivity [35]. A decrease in the mean HbA<sub>1c</sub> level was also observed, but the mean fasting plasma glucose level remained unchanged. Similarly, an increased insulin sensitivity, leading to increased glucose storage, was demonstrated after enalapril treatment in a 4 week double-blind placebo-controlled study conducted in NIDDM patients with hypertension [36].

Thus, there are obvious discrepancies between findings concerning ACE inhibitors on the glycaemic control in clinical settings and on insulin sensitivity, measured by the euglycaemic clamp or comparable methods. Although the various ACE inhibitors may have different effects on glucose metabolism, there is no convincing evidence for this. One important factor may be that most clinical studies have been performed on only a few patients. In the present study, the minimal relevant difference in HbA<sub>1c</sub> level was considered to be 0.3% and the sample size required to detect such a difference, with 5% significance and 80% power, was calculated to be 64. However, the SD of HbA<sub>1c</sub> in our study was considerably greater than expected when the study was planned. Under these circumstances, 1024 patients would be required to detect the difference of 0.3% between the groups. Only a few studies seem to have more than 20 patients, although the SD of HbA<sub>1c</sub> has ranged from 1 to 3%, both in studies which have shown and those which have not shown an effect on HbA<sub>1c</sub>. An obvious and related explanation is that measurements of insulin sensitivity by clamp or comparable techniques permit detection of changes in glucose metabolism in much smaller patient groups. Thus, in a controlled study conducted in 10 non-obese patients with essential hypertension, cilazapril treatment did not improve the oral glucose tolerance, although the insulin sensitivity, measured by the somatostatin-insulin infusion test, increased significantly [37]. At present, the mechanisms underlying the improvement in insulin resistance, demonstrated in non-diabetic and NIDDM, subjects remain unknown. Structural and functional normalization of the alterations in the resistance arteries found in patients with essential hypertension have been demonstrated

after long-term treatment with ACE-inhibitors but not after beta-adrenergic blocking agents [38, 39].

In the present study, the glucose tolerance and the C-peptide and insulin responses to glucose decreased during beta-adrenergic blockade. Beta-adrenergic blocking agents have been found to increase insulin resistance. However, a reduced insulin secretion due to beta-adrenergic blockade may also contribute (for review, see [4]). In the present study, the decrease in the C-peptide and insulin responses to a glucose load may have various explanations, such as a direct effect of metoprolol, progression of diabetes and a decrease in insulin release, secondary to increased hyperglycaemia.

Quinapril treatment was not associated with changes in the serum levels of triglycerides, cholesterol, LDL cholesterol or HDL cholesterol. However, in the metoprolol-treated patients, there was a modest but significant increase in the serum triglycerides, which correlated with the rise in HbA<sub>1c</sub>, thus suggesting that it was related to the deterioration in glycaemic control. In contrast, no changes in lipoprotein (a) concentrations occurred, which agrees with previous findings in NIDDM (for review, see [40]).

Several studies, particularly those carried out over a long-term, have shown that ACE-inhibitors reduce urinary albumin excretion in hypertensive [41–43] and normotensive [43–46] NIDDM patients. The effects of ACE-inhibitors were seen, whether or not the patient had microalbuminuria or macroalbuminuria, according to a recent meta-analysis [47]. Since it has been shown that alterations in albumin excretion are strongly related to those in glucose metabolism [48–51], the deterioration in glycaemic control, particularly in the metoprolol-treated patients, may partly explain the lack of an anti-albuminuric effect.

In choosing first-line drugs to lower blood pressure, it is important to consider the effect/side-effect balance. In this study, the impact of two therapies on subjective side-effects was evaluated with an established quality of life instrument, the so-called ASPECT scale, in relation to the antihypertensive efficacy and the metabolic control in diabetic patients with elevated blood pressure. In another report on hypertensive patients, captopril was found to have a more favourable effect on quality of life than propranolol or methyldopa [52]. However, more recently, using similar quality of life parameters and comparing ACE-inhibitors with newer beta-blockers,

such as atenolol, the effect of treatment had little, if any, effect on the perception of overall wellbeing [53–57].

The ASPECT scale is sensitive enough to detect differences concerning quality of life both between drugs and between different dose levels of a single drug [29, 30]. It is therefore of interest to note that in this study neither of the drugs changed the overall perception of well-being, as regards global well-being or total symptom ratings. There were no significant differences between quinapril and metoprolol in this respect at the end of the treatment period. However, regarding specific symptoms, the ACE inhibitor, as expected, increased the prevalence of cough, whereas treatment with the beta blocker was associated with an increased prevalence of cold digits. Somewhat unexpectedly, we found no differences between therapies concerning fatigue, physical capacity, sleep disturbances, insomnia, vivid dreams or nightmares. Metoprolol, however, induced muscle fatigue, taste disturbances and sweating, which was not the case with quinapril. Several symptoms were affected in different directions, without reaching significance (Fig. 3). Although metoprolol seemed to induce more adverse effects on certain subjective symptoms, it is important to consider all the effects on subjective symptom ratings, in view of the fact that overall well-being and total symptom scores did not change with either of the drugs. The effects on quality of life measurements must be balanced against the effects of the two therapies on metabolic control and blood pressure. Furthermore, the number of patients are too few to evaluate the effects on the quality of life and the results must therefore be interpreted with caution.

## Conclusions

In this investigation conducted in NIDDM patients, who were not treated with insulin and whose antidiabetic treatment was not changed, and who were treated with either quinapril or metoprolol over 6 months, we found a rise in the HbA<sub>1c</sub> level. This seems only in part attributable to the progress of the diabetes, since further signs of deterioration in glycaemic control (i.e. increased fasting blood glucose, decreased oral glucose tolerance and decreased C-peptide and insulin responses to a glucose challenge) were observed only in patients treated with metoprolol.

## Acknowledgements

This study received the financial support from the Parke Davis Company.

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Received 10 March 1997; accepted 23 December 1997.

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## Appendix

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