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Renal and metabolic effects of 1-year treatment with ramipril or atenolol in NIDDM patients with microalbuminuria

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Summary The clinical importance of selection of different antihypertensive drugs for the treatment of diabetic patients is still unclear. Thus we performed a randomised, controlled study in 105 hypertensive non-insulin-dependent diabetic (NIDDM) patients with microalbuminuria over 1 year. Patients received either the angiotensin converting enzyme (ACE) inhibitor ramipril (2.5–5.0 mg/day; in addition 24 % of patients also received felodipine) or the beta blocking agent atenolol (50–100 mg/day; in addition 24 % of patients also received hydrochlorothiazide). Blood pressure, metabolic control, lipid levels and albumin excretion rate were studied during the follow-up. After 1 year an almost identical fall ($p < 0.001$) in blood pressure was observed with ramipril (170/100 vs 150/85 mmHg, median) and atenolol (180/100 vs 150/80 mmHg, median). With ramipril a reduction of total cholesterol (6.3 vs 5.9 mmol/l), of LDL cholesterol (3.8 vs 3.6 mmol/l) and HDL cholesterol (1.3 vs 1.2 mmol/l) was found, whereas triglycerides slightly increased (1.8 vs 2.0 mmol/l). With atenolol a similar reduction of total cholesterol (6.3 vs 5.9 mmol/l), LDL cholesterol (3.8 vs 3.7 mmol/l) and HDL cholesterol (1.4 vs 1.2 mmol/l) and an increase of triglycerides (1.4 vs 1.7 mmol/l) was noted. Metabolic control of the patients was maintained with both ramipril and atenolol treatment. With ramipril treatment urinary albumin creatinine ratio (14.4 vs 13.8 mg/mmol) and creatinine clearance (82 vs 84 ml/min) were constant, but with atenolol an increase of albumin creatinine ratio (13.9 vs 19 mg/mmol, $p < 0.001$) and a slight decrease of creatinine clearance (80 vs 66 ml/min, $p < 0.05$, not significant after Bonferroni correction) was observed. In conclusion: 1-year treatment of NIDDM patients with ramipril or atenolol does not influence metabolic control, the changes in serum lipids were similar. Despite almost identical blood pressure reduction in both groups the albumin creatinine ratio was constant under ramipril, but increased under atenolol treatment. [Diabetologia (1996) 39: 1611–1616]

Keywords Microalbuminuria, nephropathy, NIDDM, ACE inhibitors, hypertension.

Microalbuminuria in non-insulin-dependent diabetes (NIDDM) is predictive for the later development of overt proteinuria [1] and is associated with a high mortality predominantly from cardiovascular events [1–4].

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Abbreviations: ACE, Angiotensin converting enzyme; WHO, World Health Organisation; BMI, Body mass index; NIDDM, non-insulin-dependent diabetes mellitus; GFR glomerular filtration rate.

In insulin-dependent diabetes (IDDM) hypertension contributes to the progression of diabetic nephropathy [5] but blood pressure is usually normal in the absence of renal disease and tends to rise in close relation with increasing albumin excretion rate [6, 7]. In NIDDM the temporal relationship between the onset of hypertension and the increasing albumin excretion rate is more variable; however, in the presence of diabetic nephropathy elevated blood pressure may promote the deterioration of kidney function [8, 9].

Predominantly in IDDM, it has been demonstrated that treatment with different types of antihypertensive agents can reduce albumin excretion rate

and retard the progression of diabetic nephropathy [10–15]; nephroprotective effects have also been observed with diuretics and beta blockers [16, 17]. Concerning the choice of antihypertensive treatment, specific renal protective effects have been reported for angiotensin converting enzyme (ACE) inhibitors which are metabolically neutral [18–20]. Also, Ca^{++} antagonists may reduce the urine albumin excretion rate [21–24] and have no adverse metabolic effects in contrast to diuretics and beta blockers [25–27]. Long-term studies, however, directly comparing different antihypertensive agents are scarce in NIDDM patients with microalbuminuria.

Therefore, we investigated the renal and metabolic effects of treatment with the ACE inhibitor ramipril (alone or in combination with felodipine) in comparison to the beta blocker atenolol (alone or in combination with hydrochlorothiazide) in a prospective long-term study in a representative number of NIDDM patients with microalbuminuria.

Table 1. Baseline characteristics of the population studied

	Ramipril	Atenolol
n	46	45
Sex (male/female)	17/29	10/35
Age (years)	66 (62–72)	68 (61–72)
Body mass index (kg/m^2)	27.8 (25.2–30.8)	29 (27–31.2)
Serum creatinine (μmol/l)	88.4 (79.6–106.1)	88.4 (79.6–97.2)
Duration of hypertension (years)		
< 1	9 %	18 %
< 3	4 %	9 %
< 5	26 %	22 %
> 5	61 %	51 %
Duration of NIDDM (years)		
< 1	4 %[a]	25 %[a]
< 3	28 %	20 %
< 5	11 %	13 %
> 5	57 %	42 %

[a] $p < 0.05$ (ramipril vs atenolol; Pearson chi-square test, not significant after correction according to Bonferroni)
Values are median (ranges: Quartiles Q 25–Q 75)

Patients and methods

Patients were treated for 1 year in a prospective, randomised, controlled open trial. The patients included were selected in our out-patient unit in collaboration with general practitioners.

The patients were randomised into groups of four and the same procedure was used for each centre. The definition of hypertension was in accordance with the criteria of the World Health Organisation namely systolic blood pressure over 160 mmHg and/or diastolic blood pressure 95 mmHg or more on more than one occasion. We studied 105 patients with NIDDM (age between 40 and 80 years) with mild to moderate essential hypertension (diastolic blood pressure between 95 and 114 mmHg, systolic blood pressure < 200 mmHg on more than one occasion) and microalbuminuria (24–200 mg albumin/g creatinine corresponding to 2.7–22.6 mg albumin/mmol creatinine in at least two out of three urine samples of the first voided morning urine without evidence of bacterial infection). From 380 patients originally screened for albumin/creatinine ratio, 105 presented microalbuminuria (as defined above). The clinical characteristics of the patients who completed the study, subdivided according to the antihypertensive treatment, are given in Table 1, baseline levels of blood pressure and albumin excretion in Table 2 and the metabolic characteristics in Table 3.

As demonstrated all the data in the two treatment groups were similar (except for the increased number of patients with a diabetes duration of less than 1 year in the atenolol group). The patients included had not been treated for hypertension or were not adequately treated with a monotherapy (systolic blood pressure $\geq$ 160 and/or diastolic blood pressure $\geq$ 95 on more than one occasion). Patients with secondary hypertension, electrolyte disorders, severe renal or liver failure, hypertensive encephalopathy, stroke, recurrent transient ischaemic attacks, clinical signs of heart failure, myocardial infarction in the previous 6 months or unstable angina pectoris, obstructive lung disease or asthma, abuse of drugs or alcohol, were excluded. Furthermore, none of the patients received insulin treatment or medication (including other antihypertensive drugs) that might interfere with the results of the study. Three urine samples were obtained from the patients for the determination of albumin/creatinine ratio at baseline (before treatment) and at the end of treatment period (on antihypertensive therapy), the mean values were further analyzed. Patients then provided one 24-h urine collection for the determination of creatinine clearance at baseline and after the treatment period. Antihypertensive pretreatment was stopped at least 2 weeks before inclusion in the study. Blood pressure and heart rate were documented in the sitting position after a 5-min rest at least three times on each occasion (mean values were further analysed). Blood pressure was measured with an automated sphygmomanometer cuff (Rivaton EL) at approximately the same time of day on the same arm and by the same observer. Blood pressure and urinary albumin/creatinine ratio were stable before inclusion in the study. Patients were randomly assigned to treatment with either ramipril or atenolol. The blood pressure goals were a maximum diastolic blood pressure of 90 mmHg and a maximum systolic blood pressure of 140 mmHg, or a reduction in systolic blood pressure of at least 10 mmHg on more than one occasion.

The group on ramipril started with 4 weeks of therapy at 2.5 mg, the dosage was increased to 5 mg for a further 4-week period if diastolic blood pressure was above 90 mmHg. Following this period combination therapy with 5 mg felodipine was started if diastolic blood pressure was still above 90 mmHg. After 12 months 46 % of the patients were treated with 2.5 mg ramipril, 30 % with 5 mg ramipril and in 24 % a combination with felodipine was used.

The group with atenolol started with a dosage of 50 mg atenolol, according to the same design the dosage was increased after 4 weeks to 100 mg and after a further 4-week interval combination therapy with 25 mg hydrochlorothiazide was started. After 12 months 56 % of the patients received 50 mg atenolol, 20 % received 100 mg atenolol and 24 % of the patients also received 25 mg hydrochlorothiazide.

After baseline investigations the patients were seen at 4-week intervals (weeks 4, 8, 12, 16) for the determination of blood pressure and titration of antihypertensive treatment. After that period, patients were seen at least at 3-month intervals, by the same general practitioner, for measurement of blood pressure using the same standard technique after specific instruction, documentation of side-effects and routine clinical investigations.

Ten patients on ramipril and 6 patients on atenolol treatment were withdrawn from the trial for the following reasons:

errors in ramipril dosage ($n = 2$), additional antihypertensive treatment (four patients on ramipril, one patient on atenolol therapy), normotensive blood pressure levels at baseline ($n = 1$ on atenolol). Adverse events causing withdrawal were observed in four patients on ramipril (increase of diastolic blood pressure, palpitations plus vertigo, and, in two patients, chronic cough); in four patients on atenolol (increase of diastolic blood pressure, vertigo plus hypotension, vertigo, dyspnoea and cough).

Drug-related side-effects – not causing exclusion from the study – were rare: in the patients on ramipril, palpitations (one patient), slight peripheral oedema (one patient), and cough (one patient) were observed; in the patients on atenolol dyspnoea plus arthralgia (one patient). Safety parameters (routine blood chemistry including full blood count and serum creatinine) were analysed at 3-month intervals. All patients gave informed consent and the study was performed in accordance with the Declaration of Helsinki and with local legal requirements. All blood and urine samples were collected by a clinical monitor and analysed in one central laboratory.

Body mass index (BMI) was calculated as (weight) kg/(height) m^2. Mean arterial blood pressure was calculated as diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressure (standard formula). Creatinine clearance ($ml \cdot min^{-1} \cdot 1.73\,m^2$) was calculated by amount of creatinine in urine × urine volume in 24 h × 1.73/(serum creatinine × 24 × 60 × body surface area).

Urinary albumin concentration was measured by an immunoturbidimetric test for the quantitative determination of human albumin in the urine (Tina quant) using the BM Hitachi 704/717 system. HbA_{1c} was measured by high pressure liquid chromatography, plasma glucose, creatinine and serum lipid concentrations with standard laboratory techniques.

Statistical analysis

As the variables were not normally distributed, the data are shown as median values and quartiles (Q 25–Q 75) unless otherwise stated. Urine concentration of albumin (mg/mmol creatinine), creatinine clearance and mean blood pressure were defined as the main criterion variables. Using the method of Bonferroni, the level of significance was adjusted from $\alpha = 0.5$ to $\alpha = 0.01667$ for assessment of these variables.

Non-parametric statistical tests were employed to test the main criterion variables: the signed-rank matched-paired Wilcoxon test was used for comparison of baseline data to the results after 1 year within each group. The Mann-Whitney U test and the Pearson chi-square test respectively were used for comparisons between the treatment groups at baseline and after 12 months.

The same statistical tests were used for the other variables (BMI, pulse rate, metabolic parameters plus serum lipids), the results, however, were strictly taken to be of a descriptive nature only.

Results

The effects of 12 months' therapy with ramipril and atenolol respectively, are shown in Table 2 (blood pressure, urinary albumin excretion rate, creatinine clearance) and in Table 3 (metabolic characteristics).

With both treatments we observed a significant ($p < 0.001$) reduction of systolic, diastolic and, consequently, mean blood pressure levels after 1 year. The pulse rate decreased ($p < 0.01$) with atenolol, whereas it was constant with ramipril treatment. Urinary albumin concentration (mg/mmol creatinine) was constant with ramipril therapy, whereas a significant increase ($p < 0.001$) of albumin concentration was observed in the patients on atenolol treatment. Consequently, after 1 year albumin creatinine ratio was higher in the patients on atenolol compared to the patients on ramipril treatment ($p < 0.0133$): whereas it was almost identical at baseline in the two groups. Creatinine clearance was constant with ramipril therapy: whereas a slight decrease ($p < 0.05$, not significant after correction according to Bonferroni) during atenolol therapy was noted. Serum creatinine levels were identical in the two groups of patients and did not change after 1 year of therapy (with both drugs). The renal effects of ramipril alone or ramipril plus felodipine, respectively, or atenolol alone or atenolol plus hydrochlorothiazide were not significantly different.

As shown in Table 3, fasting blood glucose, HbA_{1c} values and body weight were not significantly influenced by treatment with ramipril or atenolol – indicating that metabolic control was kept constant during the study period. We further observed a decrease of total cholesterol, HDL cholesterol and a decrease of LDL cholesterol in both groups of diabetic patients. In both treatment groups the LDL/HDL ratio was nearly constant, whereas a slight increase of triglyceride levels was observed after 1 year.

Discussion

The main findings in this study were firstly, atenolol and ramipril caused an almost identical reduction of blood pressure in a group of hypertensive NIDDM patients with microalbuminuria. This was associated with a constant albumin/creatinine ratio (and kidney function) with ramipril treatment but with a significant increase in the albumin/creatinine ratio with atenolol.

Secondly, neither ramipril nor atenolol treatment significantly influenced long-term metabolic control and both were comparable with regard to the associated alterations in serum lipid levels.

Studies directly comparing the renal and metabolic effects of ACE inhibitors, with more conventional antihypertensive agents in diabetic patients with increased albumin excretion rate, are very limited. In a recent review and meta-analysis [25], it was impossible to report a separate analysis for the use of beta blockers, diuretics or their combination because of the lack of data. Moreover, some of the studies were performed in IDDM [19, 26] and a considerable

Table 2. Blood pressure levels, urinary albumin excretion and kidney function in NIDDM subjects before and after antihypertensive treatment

Treatment	Ramipril		Atenolol	
	Baseline	12 months	Baseline	12 months
Systolic blood pressure (mmHg)	170 (160–190)	150 (140–160)[c]	180 (163–185)	150 (143–160)[c]
Diastolic blood pressure (mmHg)	100 (95–100)	85 (80–90)[c]	100 (95–104)	80 (80–90)[c]
Mean blood pressure (mmHg)	122 (117–129)	107 (103–110)[c]	124 (120–130)	107 (102–110)[c]
Pulse rate (beats/min)	74 (70–82.5)	74 (68–80)	78 (68.5–80)	70 (64–80)[b]
Urinary albumin concentration (mg/mmol creatinine)	14.4 (11.1–17.5)	13.8[d] (11.7–17.4)	13.9 (9.4–18.9)	19 (12.6–22.4)[c, d]
Creatinine clearance (ml/min)	82 (62–104)	84 (72–102)	86 (62–99)	67 (59–90)[a]

Baseline vs 12 months
[a] $p < 0.05$ (not significant after Bonferroni correction)
[b] $p < 0.01$; [c] $p < 0.001$
[d] $p < 0.01667$ (ramipril vs atenolol, α Bonferroni correction)
Values are medians (Quartiles Q 25–Q 75)

Table 3. Metabolic characteristics of NIDDM subjects before and after antihypertensive treatment

	Ramipril		Atenolol	
	Baseline	12 months	Baseline	12 months
Fasting blood glucose (mmol/l)	7.2 (5.3–9.7)	7.3 (5.3–9.7)	8.4 (5.2–9.8)	9.7 (5.9–9.1)
Haemoglobin A_{1c} (%)	7.2 (6.2–8.3)	7.4 (6.7–8.8)	7.3 (6.0–9.2)	7.2 (6.3–8.9)
Body mass index (kg/m^2)	27.8 (25.2–30.8)	27.7 (25.2–30.8)	29.0 (27.0–31.2)	28.5 (26.6–31.4)
Total cholesterol (mmol/l)	6.3 (5.1–7.2)	5.9 (5.1–7.1)	6.3 (5.5–6.6)	5.9[b] (5.1–6.7)
HDL cholesterol (mmol/l)	1.3 (1.1–1.6)	1.2[c] (1.0–1.6)	1.4 (1.2–1.6)	1.2[d] (1.1–1.5)
LDL cholesterol (mmol/l)	3.8 (3.1–4.6)	3.6[b] (2.9–4.2)	3.8 (3.3–4.3)	3.7 (3.2–4.3)
LDL/HDL ratio	3.1 (2.1–3.8)	2.9 (2.3–3.7)	2.8 (1.9–3.4)	2.8 (2.1–3.4)
Triglycerides (mmol/l)	1.8 (1.3–2.5)	2.0[a, b] (1.7–2.9)	1.4 (1.2–2.2)	1.7[a] (1.3–2.1)

Results of statistical tests are strictly of descriptive nature only:
ramipril vs atenolol: [a] $p < 0.05$
12 months vs baseline: [b] $p < 0.05$; [c] $p < 0.01$; [d] $p < 0.001$
Values are medians (ranges: quartiles Q 25–Q 75)

number of studies were performed in patients with macroalbuminuria or impaired kidney function [19, 26–28] and cannot be simply transferred to NIDDM patients with microalbuminuria with, so far, normal kidney function.

The Melbourne Diabetic Nephropathy Study Group [14] reported beneficial renal effects of 1 year's treatment with both the ACE inhibitor perindopril and with the calcium antagonist nifedipine in microalbuminuric diabetic patients. According to the study design, no comparison with more conventional antihypertensive drugs was made and the data for IDDM and NIDDM were not separated further. In normotensive NIDDM patients with microalbuminuria, albumin excretion rate plus kidney function were kept constant for 5 years with enalapril [18], whereas a deterioration was observed with placebo. In this study it was also shown that in NIDDM patients, microalbuminuria is associated with a long-term progression of kidney disease and that early medical intervention is essential. In a study in Chinese NIDDM patients with different degrees of albuminuria, an increase of albumin excretion was observed with nifedipine ($n = 10$), whereas it decreased in the enalapril ($n = 7$) treated group after 1 year [29]. It was suggested by the same author [30] that good glycaemic control may optimize the antihypertensive efficacy of ACE inhibitor therapy in (Chinese) NIDDM patients, which might partially explain some of the divergent results for ACE inhibitors in comparison with other antihypertensive agents [13, 26–29].

In our study the albumin/creatinine ratio was kept constant with ramipril which seems to reflect a specific nephroprotective effect. In other long-term

studies in microalbuminuric NIDDM patients, urinary albumin excretion only slightly decreased [14] or remained constant [18, 31], whereas an increase was observed in untreated patients or with placebo [14, 18]. Therefore it seems reasonable to conclude that the increase of urinary albumin excretion rate in our study with atenolol treatment reflects the natural course of disease. To some extent the same considerations are valid with the interpretation of kidney function in our study. Neither serum creatinine levels nor glomerular filtration rate (GFR) (creatinine clearance) changed during ramipril treatment, indicating constant kidney function and a possible beneficial effect – as previously described for other ACE inhibitors [14, 18, 31]. The slight decrease of GFR with atenolol in our study which was not statistically significant, after Bonferroni correction, has to be interpreted with caution and is probably not caused by beta blocker treatment. The determination of GFR by calculation of creatinine clearance (with inclusion of urine volume) might be less precise than the quantification by radioisotopes (Cr EDTA). In any event, a deterioration of kidney function was also noted in untreated NIDDM patients with albuminuria [18, 32]. With regard to protection of kidney function, beta blockers were found to be equally effective as ACE inhibitors in IDDM and NIDDM patients with macroalbuminuria [26, 28], whereas, in combination with a loop diuretic, a progression of diabetic renal disease was noted [27]. Furthermore, the rate of decline of GFR might slow down with an antihypertensive treatment period of longer duration. Taking these results, plus our findings, into consideration, adverse renal effects due to beta blocker treatment seem very unlikely. We have further demonstrated that both ramipril and atenolol are safe in long-term treatment, the side-effects (see Patients and methods) were relatively rare. Metabolic control was satisfactory and was not influenced significantly by ramipril or atenolol under outpatient conditions. The observed abnormalities of serum lipid in NIDDM patients with increased albumin excretion rate are in line with a previous report [33]. In accordance with recent data [26] the effects of ramipril and atenolol on lipid levels (including HDL and LDL cholesterol) were similar (despite some discrepancies in the descriptive statistical significance). In conclusion, our data suggest that in hypertensive NIDDM patients with microalbuminuria, 1-year's treatment with ramipril and atenolol does not influence metabolic control and has similar effects on serum lipid levels. Despite almost identical blood pressure reduction under outpatient conditions in both treatment groups, ramipril seems to be superior in retarding the progression of albuminuria and – with precautions – the decrease of kidney function. Longer treatment periods are necessary to clarify if these differences are of importance in the progression and prognosis of kidney disease in NIDDM.

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