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ARTICLE

Determinants of urinary albumin excretion within the normal range in patients with type 2 diabetes: the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study

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Abstract
Aims/hypothesis In contrast to microalbuminuric type 2 diabetic patients, the factors correlated with urinary albumin excretion are less well known in normoalbuminuric patients. This may be important because even within the normoalbuminuric range, higher rates of albuminuria are known to be associated with higher renal and cardiovascular risk.
Methods At the time of screening for the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) Study, the urinary albumin/creatinine ratio (UACR) was 0.44 mg/mmol in 4,449 type 2 diabetic patients. The independent correlates of UACR were analysed.
Results Independent correlates of UACR during baseline were (in descending order): night-time systolic BP (r_s=0.19); HbA_{1c} (r_s=0.18); mean 24 h systolic BP (r_s=0.16); fasting blood glucose (r_s=0.16); night-time diastolic BP (r_s=0.12); office systolic BP, sitting (r_s=0.11), standing (r_s=0.10); estimated GFR (r_s=0.10); heart rate, sitting (r_s=0.10); haemoglobin (r_s=−0.10); triacylglycerol (r_s=0.09); and uric acid (r_s=−0.08; all $p \leq 0.001$). Significantly higher albumin excretion rates were found for the following categorical variables: higher waist circumference (more marked in men); presence of the metabolic syndrome; smoking (difference more marked in males); female sex;

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antihypertensive treatment; use of amlodipine; insulin treatment; family history of diabetes; and family history of cardiovascular disease (more marked in women).
Conclusions/interpretation Although observational correlations do not prove causality, in normoalbuminuric type 2 diabetic patients the albumin excretion rate is correlated with many factors that are potentially susceptible to intervention.

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Keywords Albuminuria · Diabetes · Diabetic nephropathy · Epidemiology · Hypertension · Proteinuria

Abbreviations

ABPM	Ambulatory BP monitoring
ARB	Angiotensin receptor blocker
DBP	Diastolic BP
eGFR	Estimated GFR
ROADMAP	Randomised Olmesartan and Diabetes Microalbuminuria Prevention (Study)
SBP	Systolic BP
UACR	Urinary albumin/creatinine ratio
UAE	Urinary albumin excretion

Introduction

In both diabetic and non-diabetic patients, albuminuria has been recognised as an important renal and cardiovascular risk factor [1]. Although, using chemical methods, albuminuria had been detected in patients without primary renal disease more than 100 years ago [2], it was only after the introduction of immune detection methods [3] and the recognition that albuminuria is a predictor of diabetic nephropathy in type 1 and type 2 diabetes [4, 5] that there was an explosive growth of information in this field.

The issue whether there is a safe threshold value of albuminuria has recently provoked intense discussion, mainly because in both non-diabetic [6] and diabetic [7] patients, urinary albumin concentrations in the upper normal range have been found to predict both cardiovascular [6] and renal plus cardiovascular events [7] in high risk [6] and low risk [8] populations. For these and other reasons it has been proposed by some authors to abandon microalbuminuria as a diagnostic category and to treat urinary albumin excretion (UAE) as a continuous variable, much like BP or serum cholesterol concentration [9].

A great number of past and recent studies have evaluated the evolution of UAE from normoalbuminuria to microalbuminuria and its correlates in adolescent [10–12] and adult [13, 14] type 1 diabetic patients. Information on type 2 diabetic patients is scarcer and is available only for some small cohorts [15].

The ROADMAP (Randomised Olmesartan and Diabetes Microalbuminuria Prevention) Study [16] started in 2004 and provided a unique opportunity to investigate the factors which correlate with albumin excretion rates across the range of normoalbuminuric values in a large cohort of type 2 diabetic patients. Knowledge of these factors is of interest because albuminuria is correlated with cardiovascular and renal risk. It is the goal of the ROADMAP Study to provide further information on the selection of strategies for primary prevention of diabetic nephropathy.

In normoalbuminuric type 2 diabetic patients, it has already been shown that an ACE inhibitor reduces the risk of de novo onset of microalbuminuria [17], but, as recently emphasised in a Cochrane review [18], there is a deficit of information on angiotensin receptor blockers (ARBs). The aim of the ROADMAP study is to provide evidence of whether or not it is possible to prevent the development of microalbuminuria by administration of the ARB olmesartan medoxomil.

In the present study, we analysed the baseline albuminuria levels in the ROADMAP cohort and determined which factors correlate with the degree of albuminuria within the so-called normoalbuminuric range.

Methods

The design of the ROADMAP Study has been described in detail previously [16]. In the following details relating to the baseline data will be briefly summarised.

Study design and organisation ROADMAP is a randomised, double-blind, placebo-controlled, parallel-group, multicentre phase 3 study that is being conducted in 262 collaborating centres in 19 European countries. The study protocol, which complies with the principles of Good Clinical Practice and the Declaration of Helsinki, has been approved by the relevant ethics committee at each participating centre. Written informed consent was required from each patient before enrolment in the trial.

Study population The study has recruited 4,449 white patients (2,054 male and 2,395 female; age range, 18–75 years) with: type 2 diabetes (fasting plasma glucose ≥7.0 mmol/l and $HbA_{1c} \geq 6.5\%$, or treatment for diabetes); normoalbuminuria (≤35 mg [women] or ≤25 mg [men] albumin/g urinary creatinine); and at least one additional cardiovascular risk factor, including a lipid disorder defined as >5.2 mmol/l cholesterol or statin treatment, HDL-cholesterol <1.04 mmol/l, triacylglycerol >1.70 mmol/l, high systolic BP (SBP) (≥130 mmHg) and diastolic BP

(DBP) (≥80 mmHg) or antihypertensive medication, obesity (BMI≥28 m^2/kg), high waist circumference (>102 cm [men], >88 cm [women]) or smoking more than five cigarettes per day.

Exclusion criteria included documented renal and/or renal–vascular disease, estimated GFR (eGFR) <60 ml min^{-1} m^{-2}, recent cardiovascular event, severe hypertension (SBP> 200 mmHg and/or DBP>110 mmHg) and recent (<26 weeks) treatment with ARBs or ACE inhibitors. Patient recruitment commenced in 2004 and was completed in the first half of 2006.

Office BP measurements were performed between 06:00 and 11:00 hours as trough readings and made three times in the sitting position (with mean calculated) and once standing, using standardised oscillometric OMRON HEM-907 BP monitors (Omron, Stuttgart, Germany).

In 1,234 patients, 24 h ambulatory BP monitoring (ABPM) was performed at baseline visit, using BOSO TM-2430 ambulatory BP measurement devices (Boso, Jungingen, Germany). BP was recorded for a 24 h period. During the day (07:00–22:00 hours) measurements were performed every 15 min and during the night (22:00–07:00 hours) every 30 min.

The urinary albumin/creatinine ratio (UACR) and all other laboratory values were determined in a central laboratory (CRL-Medinet, Breda, the Netherlands) within 24 h after obtaining the urine and blood samples from the patient. Urinary albumin was measured using immunoturbidimetry (Roche, Basel, Switzerland).

In a screening visit the potential eligibility for the study was established by determining the UACR by morning spot urine testing. After a pre-randomisation phase (maximum duration 4 weeks) during which normoalbuminuria was confirmed by two additional independent morning spot urine tests. For the analysis of baseline values the average of three UACR spot urine samples was used.

Statistical analysis Baseline characteristics were analysed by the following descriptive statistics: for dichotomous and categorical variables absolute and relative frequencies (counts and percents) were calculated, whereby the denominator for per cents is defined as the number of patients with non-missing values.

Comprehensive data summaries were performed by means of sample characteristics for all continuous variables (*n*; missing *n*; arithmetic mean; SD; minimum, lower quartile, median, upper quartile, maximum and geometric mean if appropriate).

Correlations with albuminuria at screening were calculated for continuous variables by means of Spearman rank correlation coefficients (univariate and multivariate analysis; multivariate regression model with stepwise selection for $\log_e$ albumin/creatinine ratio) and for categorical variables by means of a Wilcoxon rank sums test (two-sided test, normal approximation of test statistics of this non-parametric test).

$$\mathrm{eGFR}\left(\mathrm{ml\ min^{-1}1.73\ m^{-2}}\right) = 16442 \times (\mathrm{PCr})^{-1.154} \times (\text{age in years})^{-0.203} (\times 0.742 \text{ for female patients}),$$

where PCr is serum creatinine measured in micromole per litre.

Results

Patient data at baseline The baseline data are summarised in Table 1. A total of 4,449 type 2 diabetic patients were included in the study: 90.3% of the patients had hyperten-

Table 1 Patient data at baseline

Characteristic	Total
Total	4,449
Women, *n* (%)	2,395 (53.8)
Age (years)	57.7±8.7 (58)
Known duration of diabetes (years)	6.1±6.0 (4.3)
Insulin treatment, *n* (%)	821 (18.5%)
Oral hypoglycaemic agents	3,752 (84.3)
HbA_{1c} (%)	7.6±1.6 (7.3)
Fasting blood glucose (mmol/l)	9.1±3.1 (8.4)
SBP (mmHg)	140.8±16.3 (140.0)
DBP (mmHg)	84.0±9.8 (84.0)
BMI (kg/m^2)	31.0±4.9 (30.5)
Central obesity, *n* (%)[a]	3,181 (71.5)
Metabolic syndrome, *n* (%)[b]	3,528 (79.3)
Current smokers, *n* (%)[c]	831 (18.7)
eGFR (ml min^{-1} 1.73 m^{-2})	84.5±16.8 (83.8)
Haemoglobin (g/l)	142±13 (141)
Triacylglycerol (mmol/l)	2.1±1.3 (1.8)
Total cholesterol (mmol/l)	5.3±1.1 (5.2)
LDL-cholesterol (mmol/l)	3.2±0.9 (3.1)
HDL-cholesterol (mmol/l)	1.2±0.3 (1.2)
Uric acid (μmol/l)	321±83 (321)
Known family history of diabetes, *n* (%)	2,194 (49.3)
Known family history of CV events, *n* (%)	1,678 (37.7)

Values are means±SD (median) for continuous variables, or *n* (%) for categorical variables

[a] High waist circumference: >102 cm in men, >88 cm in women

[b] NCEP ATP III criteria

[c] More than five cigarettes per day

CV, cardiovascular

sion, defined as a BP>130/80 mmHg or antihypertensive treatment; 67.5% of patients were receiving antihypertensive treatment; 71.6% had lipid disorders. A high percentage of the patients were overweight and had central obesity.

Albuminuria at screening In these patients the albumin/creatinine ratio in morning spot urine tests was $\log_e$ normally distributed with a median of 0.44 mg/mmol creatinine (interquartile range 0.28–0.81; Fig. 1). In men, the median was 0.41 mg/mmol creatinine (interquartile range 0.24–0.75, mean 0.58±0.78, geometric mean 0.43) and in women the median was 0.46 mg/mmol creatinine (interquartile range 0.31–0.88, mean 0.67±0.54, geometric mean 0.52).

The median uncorrected albumin concentration in morning spot urine tests in men was 4.2 mg/ml (interquartile range 2.0–7.7, mean 6.11±10.26, geometric mean 4.2) and in women 3.2 mg/ml (interquartile range 1.5–6.2, mean 5.04±5.27, geometric mean 3.6). The albumin/creatinine ratio is higher in women, as expected, because of the higher UACR exclusion values for female patients (≥3.96 mg/mmol) than for men (≥2.83 mg/mmol); however the absolute uncorrected albumin concentration is lower in women as a result of markedly lower urinary creatinine concentrations in women.

Ambulatory BP (Holter monitoring) in a sub-cohort of patients The values of 24 h ABPM prior to taking the study medication were available in a sub-cohort of 1,234 of the 4,449 patients (567 men, 667 women). The values of different ABPM variables are given in Table 2. The average BP was 139.6/81.5 mmHg, confirming the results obtained in the office BP cohort.

Correlation of albuminuria with continuous variables The correlations for different continuous variables were calculated. We found a correlation with several commonly measured variables. The strongest correlation was observed for night-time SBP and HbA_{1c} levels (Table 3 and Fig. 1a, b). eGFR was correlated as well, but the correlation was moderate (Fig. 1c). Multivariate analysis in the total cohort and in the sub-cohort of patients with ABPM confirmed that HbA_{1c} and SBP had the best correlation with UACR (Tables 4 and 5).

Correlation of albuminuria with categorical variables The correlations for a set of categorical variables were calculated. A highly significant correlation existed between the degree of UACR and variables of the metabolic syndrome, BP and female sex (Table 6).

Night-time BP as determinant of albuminuria As the night-time BP showed a high correlation in the uni- and multivariate analysis (ABPM sub-cohort), the effect of BP changes from day to night were analysed. The mean UACR was 0.63±0.53 mg/mmol in patients with an increased BP during the night and 0.54±0.44 mg/mmol in patients with an inverted BP profile (i.e. increased BP during the day; Table 7).

Discussion

This large study comprised 4,449 relatively young type 2 diabetic patients (mean age 57.7 years, range 28–75) with an average duration of diabetes of 6.1 years. At baseline they had moderately controlled median BP (140/84 mmHg), but attenuated lowering of night-time SBP (−6.8%). The median HbA_{1c} was relatively low (7.3%), but the cardiovascular risk factor profile was high (67.0% had ≥4 cardiovascular risk factors).

As evaluated by Spearman correlation coefficient analysis, the factors most strongly correlated with the variation in albuminuria within the normoalbuminuric range comprised BP variables, most strongly, night-time SBP and further BP indices: mean 24 h SBP, night-time SBP, office SBP in men (but not in women), mean 24 h DBP and office DBP as well as pulse pressure as an index of vascular stiffness [19].

The BP data are in good agreement with previous reports in smaller cohorts reported in the literature. In type 1

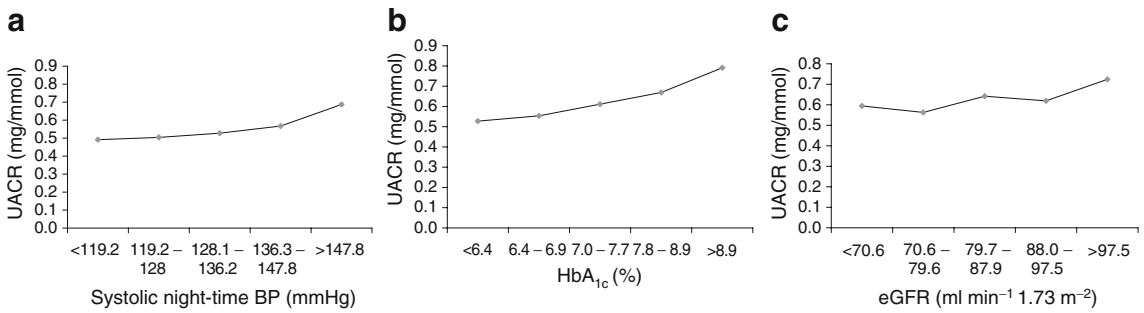

Fig. 1 Relationship of UACR with quintiles of night-time SBP (**a**), HbA_{1c} (**b**) and eGFR (**c**)

Table 2 Twenty-four hour data from ABPM

Reading	Value (n=1,234)
24 h SBP	139.6±15.4 (138.9)
24 h DBP	81.5±8.1 (81.1)
Daytime SBP	143.6±15.6 (143.4)
Daytime DBP	84.3±8.5 (83.8)
Night-time SBP	133.8±17.9 (131.7)
Night-time DBP	77.4±9.4 (6.9)
24 h pulse pressure	58.1±10.3 (57.6)
Daytime pulse pressure	59.3±10.7 (59.0)
Night-time pulse pressure	56.5±11.7 (55.1)
Mean daytime SBP minus mean night-time SBP	9.7±12.1 (10.0)
Mean daytime DBP minus mean night-time DBP	6.9±7.3 (6.9)

Values are means±SD (median)

diabetes, higher night-time SBP predicted the onset of microalbuminuria [20] and the occurrence of cardiovascular events [21], respectively. Similarly in type 2 diabetes, attenuated dipping and elevated night-time BP are frequent [22]. Night-time SBP was higher than daytime SBP in adult diabetic patients who developed microalbuminuria [22].

Table 3 Spearman rank correlation coefficients (r_s) by univariate analysis with UACR (morning spot urine) as the dependent variable

Variable	r_s	p value
Night-time SBP[a]	0.19	<0.0001
HbA_{1c}	0.18	<0.0001
Mean 24 h SBP[a]	0.16	<0.0001
Fasting glucose	0.16	<0.0001
Night-time DBP[a]	0.12	<0.0001
Mean 24 h DBP*	0.11	0.0001
Office SBP (sitting)	0.11	<0.0001
Office SBP (standing)	0.10	<0.0001
eGFR	0.10	<0.0001
Haemoglobin	−0.10	<0.0001
Triacylglycerols	0.09	<0.0001
Office pulse pressure (amplitude)	0.08	<0.0001
Uric acid	−0.08	<0.0001
Duration of diabetes	0.07	<0.0001
Office DBP (standing)	0.07	<0.0001
Office DBP (sitting)	0.06	<0.0001
BMI	0.06	<0.0001
Total cholesterol	0.05	0.0014

No univariate Spearman correlation to: ABPM SBP variability (maximum−minimum during 24 h period), LDL-cholesterol, HDL-cholesterol or neutrophil counts

[a] ABPM (Holter monitoring) data in sub-cohort of 1,234 patients

Table 4 Multivariate regression model with stepwise selection of $\log_e$ UACR

Order	Variable	Partial R^2	p value	Regression coefficient[a]
1	HbA_{1c}	0.0344	<0.0001	0.05419
2	Sex (females higher) (coded 0=male, 1=female)	0.0137	<0.0001	0.16693
3	Office SBP (sitting)	0.0126	<0.0001	0.00422
4	eGFR	0.0123	<0.0001	0.00574
5	Triacylglycerols	0.0047	<0.0001	0.03430
6	Haemoglobin	0.0034	<0.0001	−0.00420
7	Family history of diabetes	0.0028	0.0002	−0.06626
8	Age	0.0023	0.0010	0.00533
9	Heart rate (sitting)	0.0020	0.0021	0.00313
10	Antihypertensive treatment	0.0021	0.0015	0.08129
11	Smoking status (ordinally coded 0=non-smoker, 1=ex-smoker, 2=smoker)	0.0019	0.0027	0.04451
12	Fasting glucose	0.0009	0.0326	0.01034
13	HDL-cholesterol	0.0009	0.0409	−0.07907
14	Family history of CVD	0.0008	0.0436	−0.04354

[a] Variables with a positive sign for the regression coefficient, increasing albuminuria; with a negative sign, decreasing albuminuria

CVD, cardiovascular disease

Attenuated dipping was also found to be correlated with coronary events [23]. In one relatively small recent study, however, the correlation of albuminuria to night-time BP dipping was less tight than to absolute BP [24]. Furthermore, masked hypertension is also correlated with albuminuria [25]. In the present study, the ABPM sub-cohort with higher night-time than daytime BP had significantly higher (p=0.0076 by Wilcoxon rank sum test) albumin excretion compared with patients with lower night-time than daytime BP.

In a very small sample of patients with type 2 diabetes, a recent report found that pulse pressure (as a potential indicator of vascular stiffness) was related to albumin excretion [26]. This finding is confirmed in our much larger cohort. The present study, in normoalbuminuric type 2 diabetic patients, extends the findings on pulse pressure in the large cross-sectional study in microalbuminuric and proteinuric type 2 diabetic patients by Tanaka et al. [27]: the present study documents that a relationship between pulse pressure and albuminuria is found even in normoalbuminuric type 2 diabetic patients. Tanaka et al. had also noted a correlation with aortic pulse wave velocity and carotid intima–media thickness. In a small sample of normo- and microalbuminuric type 2 diabetic patients, albuminuria was correlated with markers of endothelial cell dysfunction [28], and this may explain, at least in part, this correlation to pulse wave velocity.

Table 5 Multivariate regression model with stepwise selection of $\log_e$ UACR in the sub-cohort with ABPM (n=1,234)

Order	Variable	Partial R^2	p value	Regression coefficient
1	HbA_{1c}	0.0484	<0.0001	0.08013
2	ABPM night-time SBP	0.0267	<0.0001	0.00405
3	Office SBP (sitting)	0.0103	0.0002	0.00484
4	Family history of diabetes	0.0094	0.0004	−0.14284
5	Antihypertensive treatment	0.0062	0.0037	0.14548
6	eGFR	0.0061	0.0039	0.00405
7	Sex (females higher) (coded 0=male, 1=female)	0.0047	0.0113	0.11502
8	Duration of type 2 diabetes	0.0042	0.0159	0.00063
9	Standing minus sitting office DBP	0.0031	0.0397	0.00768
10	Standing minus sitting office heart rate	0.0031	0.0372	−0.00815

In the present study albuminuria was also significantly correlated with indices of glycaemic control, i.e. HbA_{1c}, fasting glucose and duration of diabetes, as well as insulin treatment as a categorical variable. Individuals requiring insulin treatment and individuals with longer duration of diabetes presumably have more advanced renal lesions.

Furthermore, BMI and the categorical variables of elevated waist circumference and the metabolic syndrome according to NCEP-ATP-III criteria [29] were correlated with albuminuria as well. This observation is again in line with previous communications and the observation that UAE reflects insulin resistance [30].

In the general non-diabetic population [31] and in essential hypertension [32] impaired glucose tolerance increases the risk of microalbuminuria. Even sub-diabetic glycaemia increased the risk of microalbuminuria in the 'Framingham Offspring' study [33]. In the UKPDS study, the patients who presented with type 2 diabetes and had lower glycaemia had also a lower risk of albuminuria [34]. In the Australian Diabetes, Obesity and Lifestyle Study [35], the prevalence of albuminuria increased significantly with increasing glycaemia. It is particularly postprandial glycaemia, not measured in the present study, which is best correlated with albuminuria [36], so that the overall impact of glycaemia may even have been somewhat underestimated in the present study.

In the general population the metabolic syndrome is associated with both microalbuminuria and chronic kidney disease [37] and the same is observed in hypertensive patients [32].

In the general non-diabetic population, waist circumference, an index of visceral obesity, also predicted higher albumin excretion [38]. In type 1 [39] and type 2 diabetes as well [40], waist circumference had been found to be a predictor of microalbuminuria.

In the above study a positive relationship was found between albuminuria and estimated GFR [41], indicating that hyperfiltration presumably plays a role in the pathogenesis of high normal albuminuria in type 2 diabetes. A note of caution is appropriate, however, since in diabetic

Table 6 Correlation of UACR with categorical variables

Variable	Effect on albuminuria	p value[a]
Increased waist circumference	Higher	<0.0001
Men >102 cm	Higher	0.0171
Women >88 cm	Higher	NS
Metabolic syndrome (yes) (NCEP-ATP-III)	Higher	<0.0001
Female sex	Higher	<0.0001
Family history of diabetes	Lower	0.0068
Family history of CVD	Lower	0.0252
Antihypertensive medication	Higher	<0.0001
Amlodipine treatment	Higher	<0.0001
Insulin treatment	Higher	0.0280
Office SBP >140 mmHg or DBP >90 mmHg	Higher	<0.0001
Office SBP >130 mmHg or DBP >85 mmHg	Higher	<0.0001
Smoking: male ex-smokers vs non-smokers and smokers	Higher	0.0002

Categorical factors that were not significant included: family history of renal disease, family history of hypertension, current use of aspirin or statins, ethnic origin, smoking in women

[a] Two-sided Wilcoxon rank sum test; normal approximation of test statistics

CVD, cardiovascular disease

Table 7 UACR (mg/mmol) in patients (ABPM sub-cohort) with night-time SBP lower or higher than daytime SBP

Data	SBP at night ≤SBP in day (n=1,001)	SBP at night ≥SBP in day (n=229)	Total (n=1,230)
Mean±SD	0.54±0.44	0.63±0.53[a]	0.55±0.46
Q1/median/Q3	0.26/0.37/0.68	0.31/0.45/0.82	0.27/0.42/0.68
Minimum to maximum	0.11–3.42	0.11–4.03	0.11–4.03

[a] p=0.0076 vs SBP at night ≤SBP in day

Q, quartile

patients eGFR is not a reliable indicator of true GFR, at least in individual patients [42].

In agreement with reports in the literature on patients with type 1 [43] and type 2 diabetes [44], albuminuria was also correlated, although not markedly, to triacylglycerol, total cholesterol and LDL-cholesterol.

A recent report found a positive correlation between uric acid and albuminuria in male type 2 diabetic patients [45] in whom confounding factors had been excluded, such as use of allopurinol, diuretics or alcohol consumption. In the present ROADMAP Study the correlation was negative and this persisted even when adjusted for the potential confounding effect of alcohol use.

The use of and presumably need for antihypertensive medication, particularly amlodipine, was positively related to albuminuria. The correlation with antihypertensive medication may be an example of confounding by indication, i.e. that patients with more severe and more advanced disease required antihypertensive medication and had also higher rates of albuminuria. The significant effect of amlodipine, however, may be more complex. At the time of screening the patients had not yet received, or were off, renin–angiotensin receptor blockers for at least 6 months.

The strength of our study is that we analysed UACR in a large sample of type 2 diabetic patients without kidney disease (no microalbuminuria, eGFR>60 ml min^{-1} 1.73 m^{-2}). As the inclusion and exclusion criteria were fulfilled by the majority of the screened patients, this study population is representative of the majority of type 2 diabetic patients. Moreover, our data on UACR are based on the measurement of albuminuria in three morning spot urines.

It should be noted that only 10% of the total variance of the UACR could be explained by the degree of blood glucose control, BP variables, lipids and age. Verhave et al. analysed the correlation of albumin excretion (UAE) with cardiovascular risk factors in 7,841 patients of the PREVEND cohort [45]. In their cohort, taken from the general population, only 3.5% had diabetes and 14% microalbuminuria at baseline. They found a correlation between UAE and male sex, age, SBP, DBP, fasting glucose levels, BMI, smoking and creatinine clearance. In a multivariate analysis only 22% of the variance of UAE could be explained by these variables. In the PREVEND cohort the strongest correlation existed between glucose level and UAE. Since all patients in the ROADMAP Study had diabetes, this observation might explain why we were only able to explain 10% of the variance of the $\log_e$ UACR. The relatively modest correlation may also be because of the fact that most of the patients were in the low normoalbuminuric range at baseline. In this low range the variability is known to be relatively high. The intra-individual variability of the three repeated UACR measurements was 55% in the ROADMAP cohort.

Therefore, the correlation observed points more to the direction (thus providing a potential target of treatment) rather than reflecting the magnitude of the relationship. The

Table 8 Determinants of baseline values for the development of microalbuminuria

Value	Study		
	Direct [49][a]	Hope [50][b]	Benedict [17][c]
Age	n.d.	+	n.d.
Male sex	+	+	n.d.
SBP	n.d.	+	=
DBP	n.d.	=	=
Pulse pressure	n.d.	n.d.	=
BMI kg/m^2	n.d.	+	n.d.
Cholesterol	n.d.	=	n.d.
Low HDL-cholesterol	n.d.	=	n.d.
Smoking	n.d.	+	n.d.
Baseline UAE	+	n.d.	n.d.
Retinopathy	+	n.d.	n.d.
HbA_{1c}	+	n.d.	n.d.

n.d., not determined; +, positive correlation; =, no significant correlation

[a] The Diabetes Incidence after REnal Transplantation (DIRECT) Study: 3,326 and with type 1 and 1,905 type 2 diabetes were followed for 4.7 years

[b] The Heart Outcomes Prevention Evaluation (HOPE) Study: 9,043 patients with and without type 2 diabetes were followed for 4.5 years and determinants of albuminuria assessed

[c] The Bergamo NEphrologic Diabetes Complications Trial (BENEDICT): 1,204 patients with type 2 diabetes were followed for 3.6 years and risk factors for the development of microalbuminuria analysed

identified variables correlate not only with the degree of albuminuria within the normoalbuminuric range but might also be predictors for the development of microalbuminuria (Table 8).

Studies in normoalbuminuric diabetic patients have additional limitations. First, on the one hand in diabetic patients albuminuria is certainly correlated with the severity of glomerular lesions [46], but the correlation is not strict, particularly in type 2 diabetes [47]. Albuminuria therefore does not permit conclusions with respect to diabetic glomerular lesions. On the other hand, diabetic glomerular lesions may even precede the onset of albuminuria [11].

Second, microalbuminuria is present in 16% of patients at the time of diagnosis of type 2 diabetes [47]. Microalbuminuria frequently precedes the onset of overt type 2 diabetes [35] and one potential explanation may be the relatively strong correlation between albuminuria and the metabolic syndrome, a prediabetic state with insulin resistance [48].

In conclusion, the present baseline data of the ROADMAP Study suggest that albuminuria is a continuous variable, and that even in normoalbuminuric type 2 diabetic patients albumin excretion rates are correlated with a number of factors which are potentially susceptible to therapeutic intervention, although certainly correlation does not necessarily imply causality.

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