Albuminuria in type 2 diabetes mellitus: from remission to progression

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ABSTRACT

Objective Albuminuria is an early marker of renal impairment and a powerful factor of progression of renal disease in type 2 diabetes (T2D). Approximately, one-third of patients with T2D have micro- or macroalbuminuria and these patients have a high risk of progression toward End Stage Renal Disease (ESRD) as well as increased cardiovascular disease. The aim of this study was to determine the prevalence of remission, regression, persistence, and progression of albuminuria, and to evaluate the impact of change in albuminuria on kidney disease and cardiovascular disease in a prospective cohort of patients with T2D. Methods This is a prospective study. The Ethics Committee of Morocco’s Mohammed V University in Rabat approved the study protocol. Inclusion criteria targeted patients who were type 2 diabetics with albuminuria > 30 mg/day, and who had been regularly followed-up in nephrology consultation for at least 36 months. Results Five-hundred twenty-four patients were included. 75.8 and 24.6% of all patients had micro- and macroalbuminuria at enrollment in the study. At the end of the study, 91, 141, 199, and 93 patients had remission, regression, persistence, and progression of albuminuria, respectively. Remission of microalbuminuria to normoalbuminuria was observed in 23.6% of cases. Regression of macroalbuminuria to micro- was observed in 29.9% of cases. Conclusion In our study, the incidence of remission and/or regression of micro- and macroalbuminuria was higher. The incidence of ESRD and the occurrence of cardiac events were greater in the regression, persistence, and progression groups than in the remission of albuminuria group.

Introduction

In type 2 diabetes mellitus (T2D), microalbuminuria is known as an early marker of kidney disease and overt albuminuria is considered as a major risk factor for progression of kidney disease.1–3 Approximately, one-third of the patients with T2D have micro- or macroalbuminuria and these patients have a higher risk of progression towards End Stage Renal Disease (ESRD), as well as increased cardiovascular disease.4 Lowering of the albuminuria is one of the most important elements in the management of diabetic kidney disease. It can be achieved with treatment or spontaneously. While the regression of microalbuminuria is relatively frequent, regression of macroalbuminuria to micro- or normoalbuminuria is rarer in T2D, even with optimized blockage of the renin angiotensin system.5,6 Does the change in albuminuria really influence the evolution of renal disease in T2D? The aim of this study was to determine the prevalence of remission, regression, persistence, and progression of albuminuria and to evaluate the impact of the change in albuminuria on kidney disease and cardiovascular disease in a prospective cohort of patients with T2D.

Methods

This is a prospective study started in January 2008 and conducted at the Reference Center for Chronic Diseases in Oujda, Morocco (Eastern Morocco). The Ethics Committee of Morocco’s Mohammed V University in Rabat approved the study protocol (University Mohamed V Souissi, Rabat). Verbal informed consent was obtained from all participants. Inclusion criteria targeted patients who had confirmed T2D and had been regularly followed in nephrology consultation for at least 36 months. T2D was diagnosed according to the criteria of the World Health Organization.7 All patients included in the study had positive albuminuria (albuminuria > 30 mg/day). Albuminuria was measured from at least two 24-h urine samples and determined as the mean of
Table 1. Comparison of clinical and biological parameters between the four groups of patients according to the evolution of albuminuria.

| Characteristics (n = 524) | Group 1 Remission albuminuria (n = 91) | Group 2 Regression albuminuria (n = 141) | Group 3 Persistent albuminuria (n = 199) | Group 4 Progression albuminuria (n = 93) | p-Value |
|--------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|---------|
| **At baseline of the study** | | | | | |
| Female, n (%) | 68 (74.7) | 89 (63.1) | 114 (57.3) | 49 (52.7) | 0.01 |
| Age at diabetes diagnosis, years* | 53 ± 11 | 51 ± 11 | 52 ± 11 | 51 ± 11 | 0.56 |
| Duration of diabetes, years* | 11 [8, 18] | 14 [10, 20] | 14 [10, 18] | 14 [9, 19.5] | 0.22 |
| Body mass index, kg/m²* | 28.6 ± 4.1 | 26.8 ± 4.9 | 28.5 ± 4.6 | 27.5 ± 4.2 | 0.25 |
| History of hypertension, n (%) | 42 (46.2) | 81 (57.4) | 114 (57.3) | 57 (61.3) | 0.18 |
| History of cardiovascular disease (ischemic heart disease, peripheral vascular disease) n (%) | 9 (9.9) | 26 (18.4) | 36 (18.1) | 13 (14) | 0.03 |
| Smokers, n (%) | 7 (7.7) | 20 (14.6) | 24 (12.3) | 13 (14.1) | 0.43 |
| Albumin excretion rate, mg/day* | 46 [39, 67] | 260 [138, 498] | 80 [54, 231] | 107 [56, 230] | <0.001 |
| Albumin excretion rate, mg/day, stages n (%) | 89 (97.8) | 79 (56) | 155 (77.9) | 74 (79.6) | <0.001 |
| Microalbuminuria (30–300 mg/day) | 2 (2.2) | 62 (44) | 44 (22.1) | 19 (20.4) | |
| Macroalbuminuria (>300 mg/day) | 88 [65,107] | 83 [42,104] | 88 [58, 106] | 84 [59, 107] | 0.53 |
| Estimated GFR by MDRD, mL/min/1.73m²* | 84 ± 1.7 | 8.3 ± 1.7 | 8.9 ± 2.1 | 8.9 ± 1.8 | 0.02 |
| **Follow-up of the study** | | | | | |
| Annual average of SBP, mmHg* | 137 ± 14 | 139 ± 15 | 142 ± 15 | 143 ± 14 | 0.04 |
| Annual average of SBP, mmHg* | 75 ± 7 | 76 ± 7 | 77 ± 6 | 78 ± 7 | 0.03 |
| Annual average of HDL-C, g/L* | 0.46 ± 0.08 | 0.47 ± 0.14 | 0.43 ± 0.07 | 0.43 ± 0.07 | 0.25 |
| Annual average of LDL-C g/L* | 1.26 ± 0.33 | 1.0 ± 0.37 | 1.19 ± 0.40 | 1.14 ± 0.33 | 0.30 |
| Annual average of Triglycerides, g/L* | 7.8 ± 1.6 | 7.9 ± 1.1 | 8.7 ± 1.2 | 8.6 ± 1.3 | <0.001 |
| Annual average of HbA1C, %* | 7.8 ± 1.6 | 7.9 ± 1.1 | 8.7 ± 1.2 | 8.6 ± 1.3 | <0.001 |
| ACEI and ARBs use, n (%) | 78 (84.1) | 131 (92.9) | 179 (99.9) | 82 (88.2) | 0.18 |
| Statin use, n (%) | 24 (26.4) | 51 (36.2) | 76 (38.2) | 40 (43) | 0.11 |
| Insulin use, n (%) | 39 (42.9) | 92 (65.2) | 119 (59.8) | 64 (68.8) | 0.001 |
| Albumin excretion rate, mg/day# | 20 [14, 24] | 90 [57, 160] | 82 [56, 210] | 240 [133, 521] | <0.001 |
| Albumin excretion rate, mg/day, stages n (%) | 91 (100) | 0 | 0 | 0 | <0.001 |
| Normoalbuminuria (<30 mg/day) | 0 | 0 | 0 | 0 | |
| Microalbuminuria (30–300 mg/day) | 0 | 118 (83.7) | 157 (78.9) | 51 (54.8) | |
| Macroalbuminuria (>300 mg/day) | 0 | 23 (16.3) | 42 (21.1) | 42 (45.2) | |
| Estimated GFR by MDRD mL/min/1.73m²# | 84 [66,105] | 86 [48,104] | 83 [56, 103] | 83 [56, 107] | 0.51 |
| End stage renal disease, n (%) | 1 (1.1) | 12 (8.5) | 7 (3.5) | 2 (2.1) | 0.009 |
| Diabetic retinopathy, n (%) | 26 (28.6) | 63 (44.7) | 86 (43.2) | 40 (43) | 0.06 |
| Ischemic heart events occurred, n (%) | 4 (4.4) | 24 (17) | 26 (13.1) | 15 (16.1) | 0.03 |
| Perioperative vascular events occurred, n (%) | 6 (6.6) | 11 (7.8) | 17 (8.5) | 5 (5.4) | 0.79 |

Notes: *Variables expressed as mean ± SD (standard deviation), #variables expressed as median IQR (interquartile range). eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Diseases; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; hypertension defined as SBP >140 mmHg and/or DBP >90 mmHg. ACEI: Angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blocker.

Data were analyzed using the Statistical Package for Social Sciences version 13.0 (SPSS, Inc., Chicago, IL). Comparison of quantitative variables between four groups was performed using analysis of variance (ANOVA) if the variable was symmetrically distributed or the Kruskal–Wallis test if the variable was asymmetrically distributed. Comparison of qualitative variables between four groups was performed using the chi-square test. All p-values were two-sided and p < 0.05 was considered statistically significant.

**Results**

A total of 524 cases of T2D were included. 75.8% and 24.6% of patients had micro- and macroalbuminuria at enrollment in the study. 62.6% and 20.4% of patients had micro and macroalbuminuria at the end of the study. Remission of microalbuminuria to normoalbuminuria was observed in 23.6% of cases. Regression of macroalbuminuria to micro- was observed in 29.9% of cases. The mean

24-h urine collections to minimize variability. Excluded from the study were those T2D patients who were pregnant, who had a single kidney, a pathology other than diabetes capable of altering renal function (renal lithiases, Polycystic Kidney Disease, prior long-standing arterial hypertension, a neoplasm, long-term use of nephrotoxic medications), ESRD on admission and/or follow-up of less than 24 months. Patients with type 1 diabetes were excluded from this study.

Cardiac events were defined by history of angina, myocardial infarction, heart failure, and/or coronary revascularization. Remission of albuminuria was defined as returning to normo-albuminuria during the follow-up period; regression of albuminuria was defined as a decrease in urinary excretion of albumin (UEA) of 50% or more from baseline. Persistent albuminuria was defined as a decrease in UEA of less than 50% from baseline or no change from baseline and progression of albuminuria was defined as an increase in UEA of 50% or more from baseline.
of albuminuria in this group was 380 ± 55 mg/day. Table 1 shows the comparison of clinical and biological parameters between four groups of patients with T2D according to the evolution of albuminuria at the time of enrollment and at the end of the study.

Discussion

While remission and/or regression of microalbuminuria has been observed in 40–50% of patients with T2D, regression of macroalbuminuria to microalbuminuria remains less frequent and regression of macroalbuminuria to normoalbuminuria is classically rare. In our study, among 127 patients with macroalbuminuria at the time of enrollment, only two patients (1.5%) had remission to normoalbuminuria and 38 patients (29.9%) had regression to microalbuminuria. However, in the series of Yokoyama et al., the 5-year cumulative incidence rates of remission of macroalbuminuria to micro- and normoalbuminuria were 58.3 and 18.5%, respectively. This abnormally high incidence was obtained after intensification of treatment for diabetes and the factors associated with progression of albuminuria.

Conclusion

The high incidence of remission and regression of macroalbuminuria to micro- or normoalbuminuria in type 2 diabetes suggests that the concept initially mentioned of the rarity of obtaining remission of macroalbuminuria is not altogether true. This result remains dependent on optimal control of the main factors associated with progression of albuminuria, such as diabetic imbalance, arterial hypertension, hyperlipidemia, smoking, and obesity.

Disclosure statement

The authors declare that they have no conflicts of interest.

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