

Normoalbuminuric renal insufficient diabetic patients: A lower risk group

Received for publication 23 January 2007 and accepted in revised form 29 April 2007.

Vincent Rigalleau, MD,PhD, (1), Catherine Lasseur, MD (2), Christelle Raffaitin, MD (1),
Marie-Christine Beauvieux, PD,PhD, (3), Nicole Barthe, PD, (4), Philippe Chauveau, MD (2),
Christian Combe, MD,PhD, (2), Henri Gin, MD,PhD, (1)

Short title: Normoalbuminuric Chronic Kidney Disease in Diabetes

Université de Bordeaux 2-Victor Segalen, 33000 Bordeaux, France
1-Nutrition-Diabétologie, 3-Biochimie, Hôpital Haut-Lévêque, Avenue de Magellan, 33600
Pessac, France
2-Néphrologie, 4-Médecine Nucléaire, Hôpital Pellegrin, Place Amélie Raba-Léon, 33000
Bordeaux, France

Corresponding author:

Vincent Rigalleau, Nutrition-Diabétologie, Hôpital Haut-Lévêque, Avenue de Magellan, 33600
Pessac, France

e-mail: vincent.rigalleau@wanadoo.fr

ABSTRACT

OBJECTIVE- About 20% of diabetic patients with Chronic Kidney Disease (CKD) detected from the new ADA recommendations (Albumin Excretion Rate (AER) >30 mg/24H or estimated Glomerular Filtration Rate (GFR) <60 mL/min/1.73m²) may be normoalbuminuric. Do the characteristics and outcome differ for subjects with and without albuminuria?

RESEARCH DESIGN AND METHODS-Eighty-nine patients with diabetes and a MDRD-estimated GFR (MDRD e-GFR) <60 underwent a ⁵¹Cr-EDTA i-GFR determination, and were followed up for 38±11 months.

RESULTS-The mean MDRD e-GFR (41.3±13.1 mL/min/1.73m²) did not significantly differ from the i-GFR (45.6±29.7). Fifteen (17%) of the subjects were normoalbuminuric. Their i-GFR did not differ from the albuminuric and from their MDRD e-GFR, although their serum creatinine was lower (122±27 μmol/L vs 160±71, p<0.05): 71% would not have been detected by measuring serum creatinine (sCr) alone. They were less affected by diabetic retinopathy, and their HDL-cholesterol and hemoglobin were higher (p<0.05 vs albuminuric). None of the CKD normoalbuminuric subjects started dialysis (microalbuminuric: 2/36, macroalbuminuric: 10/38) or died (microalbuminuric: 3/36, macroalbuminuric: 7/38) during the follow-up period (Logrank test: p<0.005 for death or dialysis), and their AER and sCr were stable after 38 months, whereas the AER increased in the microalbuminuric patients (p<0.05) and the sCr increased in the macroalbuminuric (p<0.01).

CONCLUSIONS-Although their sCr is usually normal, most of the normoalbuminuric diabetic subjects with CKD according to a MDRD e-GFR below 60 do really have a GFR below 60. However, as expected due to normoalbuminuria and other favorable characteristics, their risk for CKD progression or death is lower.

Twenty five to forty percent of patients with diabetes have kidney damage (1), and diabetes is the first cause of End Stage Renal Disease in most countries (2). The early detection of Chronic Kidney Disease (CKD) in diabetic patients is therefore of critical importance. The conventional approach for screening is the determination of the Albumin Excretion Rate (AER). However, a substantial proportion of normoalbuminuric diabetic patients may present with a reduced Glomerular Filtration Rate (GFR): their rates have been reported to be around 20% based on $GFR < 60 \text{ mL/min/1.73m}^2$ in type 2 (3), and in type 1 based on $GFR < 90$ with more advanced glomerular lesions (4). In accordance with the National Kidney Foundation (NKF) guidelines (5), this has led the American Diabetes Association (ADA) to recommend the screening of CKD in diabetic patients based both on the AER (threshold: 30 mg/24H), and the Cockcroft & Gault or MDRD (Modification of Diet in Renal Disease) equation estimated GFR (threshold: $60 \text{ mL/min/1.73m}^2$) (6).

The MDRD equation is superior to the Cockcroft & Gault: it is more accurate (7,8), more robust when glucose control is poor (9), and not biased by body weight (10), which is of considerable importance due to the frequent association of type 2 diabetes, and CKD (11), with obesity. Most of the recent reports on CKD in diabetic patients rely on MDRD-estimated GFR (12-16). This equation may however not be ideal for screening CKD, as it is known to underestimate normal and high GFR (17,18): some of the MDRD-based CKD diagnosis may stem from this underestimation (19), particularly in normoalbuminuric patients. Furthermore, the progressive nature of normalbuminuric CKD has been argued from studies based on measured GFR, reported by one group (3,20), and its association with complications relies on reports in Asian diabetic subjects, who are known to have a high incidence of CKD (14): whether this applies to MDRD-diagnosed normoalbuminuric CKD in Caucasians remains to be demonstrated.

To evaluate the significance of normoalbuminuric CKD in diabetes, we compared the isotopic GFR and serum creatinine of normoalbuminuric vs albuminuric diabetic patients with CKD according to a MDRD-estimated $GFR < 60 \text{ mL/min/1.73m}^2$. The baseline characteristics of the patients, and their outcome during a 38 months follow-up, were also compared.

METHODS

Subjects

Eighty-nine patients (49 men, mean age 64 ± 11 yrs) were recruited from the Nutrition-Diabetology and Nephrology departments of the Centre Hospitalier Universitaire de Bordeaux. The inclusion criteria were: 1-Diabetes. Twenty-two patients had type 1 diabetes, 67 type 2, 2-CKD according to a MDRD-estimated GFR (MDRD e-GFR) below $60 \text{ mL/min/1.73m}^2$, not requiring renal replacement therapy at inclusion.

The patients gave written informed consent to participate to the study, which was approved by the ethical committee of our institution. This study was supported by a clinical research program in the Bordeaux University Hospital.

Analytical methods

The AER was determined on one 24H urine collection during a short hospitalization, with a immunonephelometric analyzer (Behring Nephelometer 2) using an appropriate kit (Nantiserum VO human albumin, Dade Behring). Serum creatinine was determined on a multiparameter analyzer (Olympus AU 640: Olympus Optical, Tokyo, Japan) using the Jaffé method with bichromatic measurements according to the manufacturer's specifications, and daily calibration of the analyzer. This procedure did not change in our laboratory during the study. Clearance of the radionuclide marker was measured after intravenous injection of $^{51}\text{Cr-EDTA}$ (Cis Industries, Gif/Yvette, France).

All patients were studied in the morning at 9 am, after a light breakfast. After a single bolus of 100 μ Ci (3.7 MBq) of ^{51}Cr -EDTA, four venous blood samples were drawn at 75, 105, 135 and 165 minutes, and urinary samples were collected at 90, 120, 150 and 180 minutes, as previously described (21). The final result was the mean of the four clearance values. If for one period the urine flow was too low or if a clearance value was not within $\pm 20\%$ of the mean of the three others, this value was excluded and the mean was calculated for the other three clearances. Less than 5% of the values were excluded this way. The ^{51}Cr -EDTA radioactivity was measured in a gamma counter (COBRA 2, model 05003, Packard Instruments, Meriden, CT).

Follow-up, care and outcome

This prospective study began on June 2001. It was based on a cooperative follow-up between diabetologists and nephrologists with the establishment of a joint medical file for each patient. This cooperative follow-up was complementary and included one visit with the diabetologist every four months, and one visit with the nephrologist every year if $40 < \text{MDRD e-GFR} \leq 60 \text{ mL/min/1.73m}^2$, every four months if $20 < \text{MDRD e-GFR} \leq 40$, then one visit every one or two months if $\text{MDRD e-GFR} \leq 20$. Mean duration of the follow-up was 38 ± 11 months.

The care program objectives included glycemic control according to the French 1999 recommendations (HbA1c $< 8.0\%$, if possible 6.5% without severe hypoglycemia in type 2, and $< 7.0\%$ in type 1), but also control of associated factors such as hypertension (objective: $< 130/80 \text{ mmHg}$) and dyslipidemia (objective: LDL-cholesterol $< 1,3 \text{ g/L}$). We prescribed $0.8 \text{ g protein/kg/d}$ according to the NKF recommendations (22), except for patients with clinical signs of undernutrition or who aged 65 years and over.

The primary outcome was requirement for dialysis, or death. The secondary outcomes were the AER and serum creatinine for alive non-dialyzed patients at the end of the follow-up.

Statistical analysis

The results are expressed as mean \pm SD. The normoalbuminuric patients were compared to the albuminuric (micro- and macroalbuminuric patients) by ANOVA and unpaired Student's t tests for the continuous variables, and by Chi2 for the categorical variables, and similar analysis were performed after categorizing the subjects as normo- (AER $< 30 \text{ mg/24H}$), micro- ($30 \leq \text{AER} < 300 \text{ mg/24H}$), and macroalbuminuric (AER $\geq 300 \text{ mg/24H}$), with a Bonferroni correction. For the primary outcome (death or dialysis), prognostic curves were obtained using the Kaplan-Meier estimation method and compared by log-rank test, the patients who did not present any event (death or dialysis onset) were censored at the end of the follow-up. For the secondary outcome, the baseline and final characteristics of the patients were compared by paired Student t tests. All the analysis was performed using SPSS software, version 10.0. The significance level was fixed at $p < 0.05$.

RESULTS

Baseline characteristics (Table 1)

Eighty-nine patients were included. Their mean diabetes duration was 18 ± 10 yrs, mean MDRD e-GFR was $41.3 \pm 13.1 \text{ mL/min/1.73m}^2$ ($11-59.9$), it did not significantly differ from their isotopic GFR (45.6 ± 29.7 , $p=0.12$), although 15 subjects had an isotopic GFR higher than 60. Fifteen subjects (17%) were normoalbuminuric. The proportion of subjects whose isotopic GFR was higher than 60 was lower in the normoalbuminuric (13.3%) than the microalbuminuric (25.7%, NS by Chi-2) group. The normoalbuminuric subjects were less frequently affected by diabetic retinopathy, but they had higher HDL-cholesterol and hemoglobin levels. For these characteristics, the difference was mainly due to the macroalbuminuric group, with intermediary values in the microalbuminuric. There were also tendencies ($p < 0.07$) for more women, less cigarette smoking, fewer previous cardiac events, a lower duration of

diabetes and a higher total cholesterol level in the normoalbuminuric group. The type of diabetes, HbA1C and blood pressure did not differ.

Most of the normoalbuminuric patients (71%) had serum creatinine levels in the normal range. Despite their lower serum creatinine levels, their MDRD e-GFR did not significantly differ from the albuminuric, and the MDRD underestimation was not significant in either group ($p=0.051$ between isotopic and MDRD e-GFR in the microalbuminuric). The correlation between MDRD e-GFR and the reference isotopic measurement was even better for the normoalbuminuric group, and the accuracy of the MDRD (%estimations within $\pm 10\%$, 30% and 50% of the isotopic GFR) tended to be better for them. The coexistence of normal AER and CKD could therefore not be attributed to the MDRD underestimation of GFR in our patients.

Outcome

Primary outcome (figure)

Ten of the albuminuric patients died during the follow-up, whereas all the normoalbuminuric were alive at its end. Twelve of the albuminuric patients required dialysis during the follow-up (10 from the macroalbuminuric patients, $p<0.01$ by Chi-2), whereas none of the normoalbuminuric did. The figure shows the log survival curve, with dialysis or death as end-point.

Secondary outcome (table 2)

The second AER and serum creatinine determination was performed in all the alive non-dialyzed patients. The changes in AER, serum creatinine and MDRD e-GFR did not significantly differ according to baseline normo-, micro- and macroalbuminuria. However, normoalbuminuria persisted during the follow-up, and serum creatinine did not change in the normoalbuminuric group. By contrast, the AER increased in the microalbuminuric patients ($p<0.05$ vs baseline), and the serum creatinine increased in the macroalbuminuric ($p<0.01$ vs baseline). The MDRD e-GFR tended to decrease in the albuminuric patients ($p=0.05$), and the

comparison between baseline and final values only involved the subjects who did not have to start hemodialysis (12 albuminuric patients, none normoalbuminuric).

CONCLUSIONS

Our first objective was to find out whether normoalbuminuric diabetic might represent an artificial group, stemming from overdiagnosed CKD due to the underestimation of high GFR by the MDRD equation. The isotopic determination of GFR in our patients argues against this hypothesis: although the MDRD underestimated their GFR, the difference was slight and not significant. The proportion of subjects whose isotopic GFR was higher than 60 was indeed lower in the normoalbuminuric (13.3%) than the microalbuminuric (25.7%, NS by Chi-2) group, and the correlation between estimated and measured GFR was better in the normoalbuminuric group. Most of these patients therefore really had a GFR below 60 mL/min/1.73m², which would have been missed for 71% of them if their renal function had been assessed solely by a higher than 120 $\mu\text{mol/L}$ serum creatinine. Despite its underestimation of GFR, mainly for GFR higher than 60 (18,23), and the increase in the number of detected CKD (12,24) the use of the MDRD equation as recommended by the ADA is of interest, especially when AER is normal.

Apart from their relatively low creatinine levels, our normoalbuminuric CKD patients displayed a number of specific characteristics: a higher proportion of women, a lower duration of diabetes, a low prevalence of retinopathy (3,4), fewer smokers (25), higher hemoglobin levels (26,27), and higher HDL-cholesterol (28,29), are consistent with previous reports on the characteristics associated with the presence of an abnormal AER. As our normoalbuminuric patients were mainly women and slightly older, their low MDRD e-GFR was not unexpected: increasing age and female gender both reduce the MDRD estimation. Only a minority of these patients had diabetic retinopathy, suggesting that their renal impairment may not

be due to diabetic nephropathy. However, around one third of type 2 diabetic patients with renal-biopsy-demonstrated diabetic glomerulopathy do not have retinopathy (30). As blood pressure levels did not differ between the two groups, it seems unlikely that the low GFR of normoalbuminuric patients was due to nephroangiosclerosis; these patients were also less affected by previous cardiovascular events. However, they required as much anti-hypertensive therapy as did the albuminuric patients, which suggests that their renal impairment was not without consequence.

Although 17 is similar to the 20 normoalbuminuric patients studied by MacIsaac et al (3), the small sample size is a limitation of our study, which probably explains why the differences between AER and e-GFR changes did not reach significance. Formulae-estimations are known to underestimate the decline in GFR in diabetic patients (31). The absence of any death or dialysis onset, and the stable AER and serum creatinine, whereas AER increased in microalbuminuric, and creatinine increased in the macroalbuminuric, both significantly, are however strong indications for a better outcome in the normoalbuminuric group. It must be noticed that most of the clinical events occurred in CKD patients with macroalbuminuria. The different characteristics we found may have contributed to this better outcome: the male gender (32), a longer duration of diabetes (33), the presence of retinopathy (34), a lower hemoglobin level (32,35), and smoking (36) have all been reported to be associated with the progression of nephropathy in diabetes. However, the most probable is the persisting absence of albuminuria by itself: numerous reports have emphasized its importance for CKD progression (30,33-35,37,38) and coronary heart disease (39) in diabetes.

Some other limitations should be noted. As reflected by the scatter of the isotopic GFR in the albuminuric group (table 1), their proportion of stages 4-5 CKD was higher (26/74 vs 3/15 normoalbuminuric), which can explain that all the subjects who

had to start dialysis were albuminuric. We feel nonetheless that the few severe and terminal CKD in the normoalbuminuric group is a reflection that it is, on the whole, a rather stable condition. Silveiro et al studied the evolution over five years of ⁵¹Cr-EDTA determined GFR in 32 normoalbuminuric type 2 diabetic subjects: their GFR decline (-0.18 mL/min/month) did not differ from normal subjects (-0.14), except for 13 subjects who were hyperfiltering at baseline (-0.61) (40). Nine of our normoalbuminuric patients were treated by ACE inhibitors or ARB. Although their proportion did not differ from the albuminuric group, these treatments may have contributed to their good outcome, but we can not be sure of this because we do not know whether they had abnormal AER before the initiation of these medications. Finally, since no renal biopsy was performed in our patients, their renal impairment may not have been due to diabetic nephropathy, which would account for their better outcome (30). We however feel that whether our patients actually had diabetic nephropathy is not the issue: our purpose was to determine the outcomes in patients with diabetes and a reduced eGFR, classified as presenting CKD according to the new recommendations. 17% of such patients were normoalbuminuric in our study. Our isotopic determination of GFR confirmed that they really had GFR below 60, although most of them would have not been detected on the sole basis of their serum creatinine level. But they did not progress, and the necessity to measure eGFR by MDRD, and label these patients as having CKD, may result in adverse emotional and financial consequences. Further studies on the outcome of normoalbuminuric CKD in diabetes seem required to demonstrate that the awareness of this condition is a benefit.

ACKNOWLEDGEMENT

This study was supported by a grant from the Programme Hospitalier de Recherche Clinique 2001. We would like to thank Dr Simon Jarman for revision of the English manuscript.

REFERENCES

1. Parving HH. Renoprotection in diabetes : genetic and non-genetic risk factors and treatment. *Diabetologia* 41 : 745-59, 1998.
2. 1999 United States Renal data System Annual Report : National Technical Information Service. US Department of Health and Human Services, Springfield, VA.
3. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. *Diabetes Care* 27: 195-200, 2004
4. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients : an indicator of more advanced glomerular lesions. *Diabetes* 52: 1036-40, 2003.
5. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation Practice Guidelines for chronic kidney disease : evaluation, classification and stratification. *Ann Intern Med.* 139: 137-47, 2003
6. Kramer H, Molitch ME. Screening for Kidney disease in Adults with Diabetes. *Diabetes Care* 28: 1813-6, 2005.
7. Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu C, et al. Estimation of glomerular filtration rate in diabetic patients, Cockcroft or MDRD formula ? *Diabetes Care* 28: 838-43, 2005
8. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations in the Estimation of GFR in Health and in Chronic Kidney Disease. *J Am Soc Nephrol* 16: 459-66, 2005
9. Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P, et al. Glucose control influences Glomerular Filtration Rate and its prediction in diabetic subjects. *Diabetes Care* 29:1491-5, 2006
10. Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Chauveau P, et al. Cockcroft-Gault formula is biased by body weight in diabetic patients with renal impairment. *Metabolism* 55: 108-12, 2006
11. Ejerblad E, Fored M, Linblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and Risk for Chronic Renal Failure. *J Am Soc Nephrol* 17: 1695-702, 2006
12. Middleton RJ, Foley RN, Hegarty J, Cheung CM, McElduff P, Gibson JM et al. The unrecognized prevalence of chronic kidney disease in diabetes. *Nephrol Dial Transplant* 21: 88-92, 2006
13. Thomas MC, Tsalamandris C, MacIsaac RJ, Jerums G. The epidemiology of Hemoglobin Levels in Patients With Type 2 Diabetes. *Am J Kidney Dis* 48: 537-45, 2006
14. Kong APS, So WY, Szeto CC, Chan NN, Luk A, Ma RCW, et al. Assessment of glomerular filtration rate in addition to albuminuria is important in managing type II diabetes. *Kidney Int* 69 : 383-7, 2006
15. So WY, Kong APS, Ma RCW, Ozaki R, Szeto CC, Chan NN, et al. Glomerular filtration Rate, Cardiorenal End Points, and All-Cause Mortality in Type 2 Diabetic Patients. *Diabetes Care* 29 : 2046-52, 2006
16. De Cosmo S, Lamacchia O, Rauseo A, Viti R, Gesualdo L, Pilotti L, et al. Cigarette smoking is associated with low Glomerular Filtration Rate in male patients with type 2 diabetes. *Diabetes Care* 29 : 2467-70, 2006
17. Froissard M, Rossert J, Jacquot C, Paillard M, houiller P. Predictive Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations for Estimating Renal function. *J Am Soc Nephrol* 16: 763-73, 2005
18. Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P, et al. The Mayo Clinic Quadratic equation improves the prediction of the Glomerular Filtration Rate in diabetic subjects. *Nephrol Dial Transplant* 2006 Nov 24.

19. Rigalleau V, Lasseur C, Chauveau P, Raffaitin C, Perlemoine C, Barthe N, et al. Is the diagnosis of chronic kidney disease missed in diabetic women? *Nephrol Dial Transplant* 21:1732-3, 2006
20. Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, et al. Progressive decline in renal function in diabetic patients with and without albuminuria. *Diabetes* 43:649-55, 1994
21. Combe C, Deforges-Lasseur C, Caix J, Pommereau A, Marot D, Aparicio M. Compliance and effects of nutritional treatment on progression and metabolic disorders of chronic renal failure. *Nephrol Dial Transplant* 8: 412-8, 1993
22. National Kidney Foundation. Kidney disease outcome quality initiative. Clinical practice guidelines for nutrition in chronic renal failure. I. Adult guidelines. B. Advanced chronic renal failure without dialysis. *Am J Kidney Dis* 35: S56-S65, 2000
23. Ibrahim H, Mondress M, Tello A, et al. An alternative formula to the Cockcroft-Gault and the modification of diet in renal diseases formulas in predicting GFR in individuals with type 1 diabetes. *J Am Soc Nephrol* 16: 1051-60, 2005
24. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 289: 3273-7, 2003
25. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes* 50:2842-9, 2001
26. Thomas MC, MacIsaac RJ, Tsalamandris C, Molyneaux L, Goubina I, Fulcher G, et al. Anemia in patients with type 1 diabetes. *J Clin Endocrinol Metab* 89: 4359-63, 2004
27. Thomas MC, MacIsaac RJ, Tsalamandris C, Molyneaux L, Goubina I, Fulcher G, et al. The burden of anaemia in type 2 diabetes and the role of nephropathy: a cross-sectional audit. *Nephrol Dial Transplant* 19:1792-7, 2004
28. Jones SL, Close CF, Mattock MB, Jarrett RJ, Keen H, Viberti GC. Plasma lipid and coagulation factor concentrations in insulin dependent diabetics with microalbuminuria. *BMJ* 298:487-90, 1989
29. Niskanen L, Uusitupa M, Sarlund H, Siitonen O, Voutilainen E, Penttila I, et al. Microalbuminuria predicts the development of serum lipoprotein abnormalities favouring atherogenesis in newly diagnosed type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 33:237-43, 1990
30. Christensen PK, Gall MA, Parving HH. Course of glomerular filtration rate in albuminuric type 2 diabetic patients with or without diabetic glomerulopathy. *Diabetes Care* 23 Suppl 2:B14-20, 2000
31. Rossing P, Rossing K, Gaede P, Pedersen O, Parving HH. Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy. *Diabetes Care* 29:1024-30, 2006
32. Ueda H, Ishimura E, Shoji T, et al: Factors affecting progression of renal failure in patients with type 2 diabetes. *Diabetes Care*; 26: 1530-4, 2003
33. Bruno G, Biggeri A, Merletti F, Bargero G, Ferrero S, Pagano G, et al. Low incidence of end-stage renal disease and chronic renal failure in type 2 diabetes: a 10-year prospective study. *Diabetes Care* 26:2353-8, 2003
34. Trevisan R, Vedovato M, Mazzon C, Coracina A, Iori E, Tiengo A, et al. Concomitance of diabetic retinopathy and proteinuria accelerates the rate of decline of kidney function in type 2 diabetic patients. *Diabetes Care* 25:2026-31, 2002
35. Babazono T, Hanai K, Suzuki K, Kiuchi Y, Inoue A, Tanaka M, et al. Lower haemoglobin level and subsequent decline in kidney function in type 2 diabetic adults without clinical albuminuria. *Diabetologia* 49:1387-93, 2006

36. Stegmayr B, Lithner F. Tobacco and end stage diabetic nephropathy. *BMJ* 295:581-2, 1987
37. Jacobsen P, Rossing K, Tarnow L, Rossing P, Mallet C, Poirier O, et al. Progression of diabetic nephropathy in normotensive type 1 diabetic patients. *Kidney Int Suppl* 71:S101-5, 1999
38. Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH. Progression of nephropathy in type 2 diabetic patients. *Kidney Int* 66:1596-605, 2004
39. Mattock MB, Barnes DJ, Viberti G, Keen H, Burt D, Hughes JM, et al. Microalbuminuria and coronary heart disease in NIDDM: an incidence study. *Diabetes* 47:1786-92, 1998
40. Silveiro SP, Friedman R, de Azevedo MJ, Canani LH, Gross JL. Five-year prospective study of glomerular filtration rate and albumin excretion rate in normofiltering and hyperfiltering normoalbuminuric NIDDM patients. *Diabetes Care* 19:171-4, 1996

Table 1.

| | Normo albuminuric | Albuminuric | P | Micro albuminuric | Macro albuminuric |
|---|-------------------|-----------------|-------|-------------------|-------------------|
| n | 15 | 74 | | 36 | 38 |
| AER (mg/24H) | 20.7±6.2 | 712±876 | 0.003 | 123.7±78.7 | 1270±922*° |
| Serum creatinine (SCr, μmol/L) | 122±27 | 160±71 | 0.04 | 135±44 | 183±84*° |
| % SCr <120 μmol/L | 71% | 33% | 0.006 | 35%* | 30%* |
| Isotopic GFR (mL/min/1.73m ²) | 47.5±19.9 | 45.2±31.4 | 0.79 | 51.8±27.4 | 39.0±33.6 |
| MDRD e-GFR (mL/min/1.73m ²) | 45.6±8.9 | 40.4±13.7 | 0.17 | 43.8±12.2 | 37.2±14.5 |
| Correlation between MDRD e-GFR and isotopic GFR | r=0.69, p<0.005 | r=0.45, p<0.001 | | r=0.53, p<0.001 | r=0.34, p<0.05 |
| % MDRD estimations within | | | | | |
| -isotopic GFR±10% | 26% | 24% | 0.84 | 22% | 26% |
| -isotopic GFR±30% | 73% | 60% | 0.56 | 61% | 60% |
| -isotopic GFR±50% | 86% | 79% | 0.72 | 83% | 76% |
| Gender (% female) | 66% | 40% | 0.058 | 52% | 29%* |
| Diabetes type (% Type 2) | 80% | 75% | 0.48 | 73% | 76% |
| Age (yrs) | 68±9 | 64±12 | 0.17 | 65±11 | 62±13 |
| Diabetes duration (yrs) | 14±5 | 19±11 | 0.06 | 19±12 | 19±10 |
| BMI (kg/m ²) | 27.0±4.5 | 26.9±4.3 | 0.89 | 27.1±4.4 | 26.7±4.3 |
| HbA1C (%) | 9.0±1.3 | 8.5±1.6 | 0.31 | 8.6±1.3 | 8.5±2.0 |
| Cholesterol (g/L) | 2.37±0.67 | 2.10±0.48 | 0.07 | 2.03±0.38 | 2.16±0.56 |
| LDL-C (g/L) | 1.26±0.46 | 1.19±0.40 | 0.54 | 1.14±0.32 | 1.25±0.47 |
| HDL-C (g/L) | 0.64±0.28 | 0.52±0.17 | 0.04 | 0.56±0.19 | 0.49±0.15* |
| Triglycerides (g/L) | 1.91±1.86 | 1.76±1.09 | 0.67 | 1.56±0.09 | 1.96±1.23 |
| BP, systolic (mmHg) | 143±16 | 147±19 | 0.47 | 145±19 | 149±19 |
| BP, diastolic (mmHg) | 79±8 | 81±10 | 0.56 | 79±9 | 83±10 |
| Number of antihypertensive drugs | 2.5±1.8 | 2.4±1.2 | 0.68 | 2.2±1.0 | 2.5±1.3 |
| % on ACE inhibitors | 40% | 59% | 0.25 | 69% | 50% |
| % on Ang2 rec. inhibitors | 20% | 16% | 0.71 | 16% | 17% |
| Hemoglobin level (g/dL) | 13.3±1.4 | 12.3±1.4 | 0.01 | 12.6±1.3 | 12.0±1.4* |
| % with previous cardiac event | 13% | 38% | 0.058 | 31% | 46% |
| % with diabetic retinopathy | 26% | 66% | 0.01 | 61%* | 71%* |
| % cigarette smoking | 20% | 52% | 0.054 | 41% | 63%* |

*means p<0.05 vs the normoalbuminuric group, ° means p<0.05 vs the microalbuminuric group. The right column gives the significance for the difference between the normoalbuminuric group and the other (n=74) patients.

Table 2.

| | Normoalbuminuric | Microalbuminuric | Macroalbuminuric |
|---|------------------|------------------|------------------|
| | n=15 | n=36 | n=38 |
| Follow-up duration (months) | 40±8 (23-54) | 38±11 (17-54) | 37±13 (2-59) |
| AER (mg/24H) | 18.0±9.0 | 271.1±342.2* | 1508.3±417.4 |
| Serum creatinine (μmol/L) | 123±25 | 142±44 | 265±167** |
| MDRD e-GFR (mL/min/1.73m ²) | 45.8±8.5 | 43.0±12.8 | 29.5±21.1 |
| Dialysis onset | 0 | 2 | 10 °° |
| Death | 0 | 3 | 7 |

*, ** indicate p<0.05 and p<0.01 vs the result at the inclusion (shown in the table 1).

°° indicates p<0.01 by Chi-2

Figure 1

