The Presence and Consequence of Nonalbuminuric Chronic Kidney Disease in Patients With Type 1 Diabetes

DOI: 10.2337/dc15-0641

OBJECTIVE
This study investigated the prevalence of nonalbuminuric chronic kidney disease in type 1 diabetes to assess whether it increases the risk of cardiovascular and renal outcomes as well as all-cause mortality.

RESEARCH DESIGN AND METHODS
This was an observational follow-up of 3,809 patients with type 1 diabetes from the Finnish Diabetic Nephropathy Study. All patients were Caucasians and thoroughly examined at baseline. Their mean age was 37.6 ± 11.8 years, and duration of diabetes 21.2 ± 12.1 years. Follow-up data on cardiovascular and renal outcomes and mortality were retrieved from registers. During 13 years of median follow-up, 378 developed end-stage renal disease, 415 suffered an incident cardiovascular event, and 406 died.

RESULTS
At baseline, 78 (2.0%) had nonalbuminuric chronic kidney disease. This was associated with older age, female sex, history of retinal laser treatment, cardiovascular events, and the number of antihypertensive drugs in use, but not with blood pressure levels or specific antihypertensive agents. Nonalbuminuric chronic kidney disease did not increase the risk of albuminuria (hazard ratio [HR] 2.0 [95% CI 0.9–4.4]) or end-stage renal disease (HR 6.4 [0.8–53.0]) but did increase the risk of cardiovascular events (HR 2.0 [1.4–3.5]) and all-cause mortality (HR 2.4 [1.4–3.9]). The highest risk of cardiovascular and renal end points was observed in the patients with albuminuria.

CONCLUSIONS
Nonalbuminuric chronic kidney disease is not a frequent finding in patients with type 1 diabetes, but when present, it is associated with an increased risk of cardiovascular morbidity and all-cause mortality but not with renal outcomes.

Albuminuria and chronic kidney disease (CKD) are both strong risk factors for cardiovascular morbidity and mortality in patients with and without diabetes (1–4), and as expected, both are also associated with a markedly increased risk of renal outcomes (5). Albuminuria is considered an early marker of kidney damage and is used as a tool to identify patients at risk for renal disease development and progression as well as for the diagnosis of diabetic nephropathy. In type 2 diabetes, however, as many as 35–57% of the patients with CKD do not present with albuminuria (6–9). On
the basis of these findings, it is recommended that patients with diabetes should be screened annually for their estimated glomerular filtration rate (eGFR) in addition to albuminuria (10). The pathogenesis of nonalbuminuric CKD is not fully understood. Nonalbuminuric CKD has been associated with more advanced glomerular lesions compared with patients with no albuminuria and no CKD (11,12) but with significantly fewer lesions than in patients with albuminuric CKD (13). Different risk factors for the development of albuminuria and CKD have also been observed, indicating that these two at least partly reflect separate phenomena (14).

In patients with type 2 diabetes, nonalbuminuric CKD is associated with female sex, older age, and the presence of hypertension, neuropathy, and macrovascular disease (8,15). Nonalbuminuric CKD also seems to be associated with a more favorable long-term prognosis compared with albuminuric CKD but is nonetheless associated with an increased risk of renal outcomes (5), cardiovascular disease (5,16), and mortality (1) compared with patients with no albuminuria and no CKD.

Less is known about nonalbuminuric CKD in patients with type 1 diabetes. In smaller studies, it has been associated with female sex and the presence of retinopathy (11,12,17) compared with patients with no albuminuria and no CKD. In larger clinical studies, nonalbuminuric CKD has been observed in 7–24% of the patients who develop sustained CKD during follow-up (18,19). However, the clinical effect of nonalbuminuric CKD in type 1 diabetes remains unexplored. Thus, our aim was to evaluate the predictive value of albuminuria and CKD for the development of end-stage renal disease (ESRD), cardiovascular events, and all-cause mortality. Another aim was to assess the prevalence and factors associated with nonalbuminuric CKD in Finnish patients with type 1 diabetes.

**RESEARCH DESIGN AND METHODS**

This study is part of the Finnish Diabetic Nephropathy (FinnDiane) Study, which is a nationwide multicenter study with the aim to identify genetic, clinical, and environmental risk factors for micro- and macrovascular complications of type 1 diabetes. The study design is an observational prospective study, and a detailed description of the research design and the population has previously been reported (2,20). In brief, patient recruitment was initiated in 1997, and 89% of baseline visits were conducted in the years 1998–2005. All patients are Caucasians and were enrolled in connection with a regular visit to their attending physician. At baseline, the attending physicians and the patients completed questionnaires regarding the patients’ medical condition, medical history, and lifestyle. For the current study, we included all patients in the FinnDiane database with type 1 diabetes, without ESRD, and with complete information available on albuminuria status and eGFR at baseline (n = 3,809). The study protocol was approved by the local ethics committee at each study center, and the study was performed in accordance with the Declaration of Helsinki. Each participating patient signed a written informed consent.

Type 1 diabetes was defined as a diabetes diagnosis before 40 years of age and insulin medication initiated within 1 year of the diabetes diagnosis. Serum samples were analyzed for HbA1c, lipids, lipoproteins, and creatinine. Each patient collected timed urine samples for the measurement of the urinary albumin excretion rate, and albuminuria status was based on measurements from two of three overnight or 24-h urine collections. Albuminuria was defined as a urinary albumin excretion rate ≥20 μg/min or ≥30 mg/24 h. The eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula (21). CKD was defined as eGFR <60 mL/min/1.73 m². Patients were divided into four groups according to the presence or absence of albuminuria and CKD: nonalbuminuric non-CKD, nonalbuminuric CKD, albuminuric non-CKD, and albuminuric CKD.

Blood pressure was measured twice in the sitting position after a 10-min rest, and the mean values for systolic and the diastolic blood pressure were used. Antihypertensive medication was defined as the use of any antihypertensive agent. Types of agents in use (e.g., ACE-inhibitors or angiotensin receptor blockers [ARBs]), were recorded. History of cardiovascular event included a history of myocardial infarction, coronary revascularization, or stroke. Smoking was defined as smoking at least 1 cigarette per day for at least 1 year.

**Follow-up Data**

Follow-up data for the patients were retrieved by the end of 2013. Follow-up data on ESRD and cardiovascular events were retrieved from the Finnish national hospital discharge register Care Register for Health Care. ESRD was identified based on initiation of dialysis. Cardiovascular events included myocardial infarction, coronary revascularization, stroke, or death from a cardiovascular cause during follow-up. Myocardial infarction was identified based on ICD-9 codes 410–412 and ICD-10 codes I21–I23. Strokes were identified based on ICD-9 codes 430–434 and ICD-10 codes I60–I63. Coronary revascularization was identified from the discharge register based on a separate surgical procedure classification system. Information on vitality status and causes of death was retrieved from Statistics Finland. Death certificates were available for 387 of the patients (95%) who had died. Death from a cardiovascular cause included any cardio- or cerebrovascular cause as the immediate or underlying cause of death. A total of 378 patients (9.9%) developed ESRD during a median 12.5 (10.2–14.4) years of follow-up, 415 patients (11.5%) suffered an incident cardiovascular event during 12.9 (10.2–14.8) years of follow-up, and 406 (10.7%) died during 13.1 (11.2–15.0) years of follow-up. Of patients with nonalbuminuric CKD, 19 died during follow-up. The underlying cause of death was cardiovascular in 11 patients, diabetes complications in 4 (none due to uremia), cancer in 3, and an unknown cause in 1.

**Statistical Analyses**

Parametric continuous variables were analyzed with the t test, and results are presented as means with the SD. Nonparametric variables were analyzed with the Mann-Whitney U test, and results are presented as medians with interquartile range. The difference in categorical variables between groups was tested with the χ² test. Logistic regression analysis with forward stepwise entry was performed to determine factors independently associated with CKD in patients without albuminuria. Variables were chosen for the analysis based on significant univariate associations.
The results are presented as the odds ratio (OR) with 95% CI. Cox proportional hazards analysis was performed to determine whether CKD affected the risk of albuminuria development in patients without albuminuria at baseline. The analysis was adjusted by known risk factors for albuminuria development, including diabetes duration, sex, HbA1c, systolic blood pressure, triglycerides, and smoking. In addition, Cox proportional hazards analyses were performed to determine the risk related to the four groups based on albuminuria and CKD with respect to the different end points. The analyses for risk of developing ESRD or cardiovascular events were adjusted for factors that were associated with the specific end point in univariate analyses. The analysis for risk of all-cause mortality was adjusted for age only. The results are presented as the hazard ratio (HR) with the 95% CI. P < 0.05 was considered statistically significant. Analyses were performed with IBM SPSS Statistics 22 software (IBM Corporation, Armonk, NY).

RESULTS

Of the 3,809 patients eligible for the study, 78 (2.0%) had nonalbuminuric CKD. Clinical characteristics of patients in the four groups based on presence or absence of albuminuria and CKD are presented in Table 1. Patients with nonalbuminuric CKD were more often female, were substantially older, and had a longer duration of diabetes compared with the three other groups.

Nonalbuminuric CKD Compared With Nonalbuminuric Non-CKD

In patients without albuminuria, those with CKD had higher blood pressure levels, higher HDL-cholesterol, were more frequently taking antihypertensive medication, and had more frequently a history of retinal laser treatment and cardiovascular events (Table 1). There were also fewer current smokers among these patients with nonalbuminuric CKD. Factors that were independently associated with nonalbuminuric CKD were age (OR per 1 year 1.1 [95% CI 1.1–1.1], P < 0.001), female sex (3.7 [2.1–6.7], P < 0.001), history of retinal laser treatment (2.3 [1.3–3.8], P = 0.002), history of cardiovascular events (2.2 [1.0–4.8], P = 0.045), and the number of prescribed antihypertensive drugs (OR per 1 drug 1.4 [1.0–1.8], P = 0.025), but not blood pressure levels or specific antihypertensive agents (e.g., ACE-inhibitors or ARBs).

Nonalbuminuric CKD Compared With Albuminuric CKD

Of the 520 patients with CKD, 78 (16%) did not have albuminuria. Those without albuminuria were older, had an older age of diabetes onset, lower blood pressure, better glycemic control, a more favorable lipid profile, less frequent usage of antihypertensive agents, less frequently had received retinal laser treatment, and had fewer smokers (Table 1). Factors that were independently associated with nonalbuminuric CKD in patients with CKD included age (OR per 1 year 1.1 [95% CI 1.1–1.2], P < 0.001), female sex (3.0 [1.3–6.9], P = 0.008), HDL-cholesterol (OR per 1 mmol/L 3.2 [1.4–7.3], P = 0.004), absence of retinal laser treatment (4.9 [2.2–11.1], P < 0.001), and absence of antihypertensive medication (197.8 [49.1–797.5], P < 0.001).

Development of Albuminuria

Of patients without albuminuria at baseline, 180 (7.2%) developed albuminuria. Development of albuminuria was more favorable in patients with albuminuric non-CKD (HR 0.4 [95% CI 0.2–0.8]) and in patients with albuminuric CKD (HR 0.1 [0.0–0.1]), and was the highest in those with albuminuric non-CKD (HR 7.6 [6.0–9.7]).

Development of ESRD

ESRD developed during follow-up in 0.3% of patients with nonalbuminuric non-CKD, in 1.3% of patients with nonalbuminuric CKD, in 13.9% of patients with albuminuric non-CKD, and in 63.0% of patients with albuminuric CKD (P < 0.001). The risk of developing ESRD by the four groups based on albuminuria and CKD are presented in Fig. 1. In adjusted Cox regression analysis, the risk of ESRD was the lowest in patients with nonalbuminuric non-CKD (reference, HR 1.0), and did not increase with the presence of nonalbuminuric CKD (HR 6.4 [95% CI 0.8–53.0]) but did increase significantly in patients with albuminuric non-CKD (HR 33.1 [15.1–72.8]) and further in patients with albuminuric CKD (HR 220.7 [99.5–489.2]).

Nonalbuminuric CKD Compared With Albuminuric CKD

Development of Cardiovascular Events

The risk of developing cardiovascular events by the four groups based on albuminuria and CKD are presented in Fig. 2. In adjusted Cox regression analysis, the risk of cardiovascular events was the lowest in patients with nonalbuminuric non-CKD (reference, HR 1.0) and was increased in patients with nonalbuminuric CKD (HR 2.0 [95% CI 1.4–3.5]), in patients with albuminuric non-CKD (HR 1.7 [1.3–2.3]), and even further in patients with albuminuric CKD (HR 3.1 [2.3–4.2]).

All-Cause Mortality

All-cause mortality in the four groups based on albuminuria and CKD is presented in Fig. 3. In Cox regression analysis adjusted for age, the risk of all-cause mortality was the lowest in patients with nonalbuminuric non-CKD (reference, HR 1.0), was increased in patients with nonalbuminuric CKD (HR 2.4 [95% CI 1.4–3.9]) and in patients with albuminuric non-CKD (HR 3.1 [2.4–4.1]), and was the highest in those with albuminuric CKD (HR 7.6 [6.0–9.7]).

CONCLUSIONS

In this study of 3,809 Finnish patients with type 1 diabetes, we observed that nonalbuminuric CKD is rather uncommon and present in only 2% of the study population. Nonalbuminuric CKD was associated with older age, female sex, and the presence of retinopathy and cardiovascular disease. Of the patients with CKD, 16% did not have concomitant albuminuria. Compared with the patients with albuminuric CKD, the patients with nonalbuminuric CKD had less retinopathy, less antihypertensive treatment, were older, and were more often females. A novel finding was that nonalbuminuric CKD increased the risk of cardiovascular morbidity and all-cause mortality to the same extent as albuminuric non-CKD but did not increase the risk of renal outcomes in type 1 diabetes. The highest risk of the outcomes studied was observed in the patients with albuminuric CKD. The overall prevalence of 2% of nonalbuminuric CKD in our study population is considerably lower than the 10% prevalence observed in type 2 diabetes (8,22). The lower frequency in type 1 diabetes is probably mainly due to the
lower mean age of our study population and also to the higher prevalence of hypertension and vascular disease observed in patients with type 2 diabetes (8). We could confirm earlier findings from smaller studies in patients with type 1 diabetes that nonalbuminuric CKD is associated with older age and female sex (12,17). A female predominance among patients with nonalbuminuric CKD has been observed in patients with type 2 diabetes and in the general population (7,8,14). This might be due to true differences in CKD risk between the sexes or too observed as association with the use of ACE-inhibitors or ARBs, had increased dramatically. In our study, the failure to observe an association with the use of ACE-inhibitors, ARBs, or antihypertensive treatment in general could be explained by different methodology to define albuminuria. Our study classified all patients with a known history of albuminuria as albuminuric although they might have regressed to normal albuminuria or were, however, controlled with more antihypertensive agents. This could reflect more advanced general atherosclerosis in these patients.

![Figure 1](http://example.com/image1.png)

**Figure 1**—The risk of developing ESRD by the four groups based on albuminuria and CKD, adjusted for sex, age, age at diabetes onset, systolic blood pressure, HbA1c, triglycerides, history of retinal laser treatment, history of cardiovascular event, and current smoking.

| Table 1—Clinical characteristics of patients at baseline by albuminuria status and CKD |
|---------------------------------|-------------------------------|-----------------|-----------------|-------------------------------|-----------------|-----------------|
| Nonalbuminuric non-CKD (n = 2,567) | Nonalbuminuric CKD (n = 78) | P value | Albuminuric non-CKD (n = 740) | P value* | Albuminuric CKD (n = 424) | P value* |
| Female sex (%) | 51 | 77 | <0.001 | 40 | <0.001 | 42 | <0.001 |
| Age (years) | 34.9 (26.3–43.9) | 55.1 (45.5–61.3) | <0.001 | 37.4 (30.1–46.4) | <0.001 | 43.7 (36.1–50.7) | <0.001 |
| Diabetes duration (years) | 16.4 (8.8–26.0) | 35.8 (22.8–45.7) | <0.001 | 25.2 (18.0–32.1) | <0.001 | 30.1 (24.4–35.6) | <0.001 |
| Age at diabetes onset (years) | 16.3 (10.6–25.1) | 14.7 (11.6–25.3) | 0.943 | 11.0 (6.7–16.8) | <0.001 | 12.1 (8.1–17.5) | <0.001 |
| BMI (kg/m²) | 24.8 ± 3.4 | 25.2 ± 3.3 | 0.369 | 25.8 ± 3.8 | 0.190 | 25.9 ± 4.1 | 0.139 |
| Systolic blood pressure (mmHg) | 129 ± 15 | 137 ± 20 | 0.003 | 137 ± 17 | 0.847 | 147 ± 21 | <0.001 |
| Diastolic blood pressure (mmHg) | 78 ± 9 | 75 ± 9 | 0.001 | 81 ± 10 | <0.001 | 82 ± 11 | <0.001 |
| HbA1c (%) | 8.2 ± 1.4 | 8.1 ± 1.2 | 0.514 | 8.9 ± 1.5 | <0.001 | 9.0 ± 1.5 | <0.001 |
| HbA1c (mmol/mol) | 66 ± 15 | 65 ± 13 | 0.513 | 74 ± 17 | <0.001 | 74 ± 16 | <0.001 |
| Cholesterol (mmol/L) | 4.78 ± 0.89 | 4.91 ± 0.94 | 0.181 | 5.09 ± 0.99 | 0.127 | 5.12 ± 0.99 | 0.010 |
| LDL-cholesterol (mmol/L) | 2.90 ± 0.81 | 2.91 ± 0.91 | 0.937 | 3.17 ± 0.92 | 0.018 | 3.26 ± 0.99 | 0.004 |
| HDL-cholesterol (mmol/L) | 1.38 ± 0.38 | 1.51 ± 0.46 | 0.013 | 1.31 ± 0.39 | <0.001 | 1.19 ± 0.41 | <0.001 |
| Triglycerides (mmol/L) | 0.93 (0.71–1.28) | 0.99 (0.81–1.24) | 0.168 | 1.12 (0.84–1.62) | 0.009 | 1.47 (1.08–2.24) | <0.001 |
| GFR (mL/min) | 97 (83–110) | 55 (49–58) | <0.001 | 87 (75–102) | <0.001 | 37 (23–51) | <0.001 |
| Urinary AER (mg/24 h) | 7 (4–12) | 7 (5–13) | 0.924 | 91 (36–261) | <0.001 | 471 (121–1464) | <0.001 |
| Antihypertensive medication (%) | 14 | 46 | <0.001 | 75 | <0.001 | 99 | <0.001 |
| ACE inhibitors or ARBs (%) | 11 | 29 | <0.001 | 69 | <0.001 | 86 | <0.001 |
| Other antihypertensive agents (%) | 6.9 | 32 | <0.001 | 25 | 0.431 | 79 | <0.001 |
| Antihypertensive medications used | 0 (0–4) | 0 (0–4) | <0.001 | 1 (0–5) | 0.001 | 2 (0–5) | <0.001 |
| Mean (range) | 0.19 | 0.81 | 1.05 | 2.35 |
| History of retinal laser treatment (%) | 13 | 44 | <0.001 | 55 | 0.072 | 83 | <0.001 |
| History of cardiovascular event (%) | 2.0 | 19 | <0.001 | 4.2 | <0.001 | 17 | 0.613 |
| Current smoking (%) | 23 | 12 | 0.029 | 34 | <0.001 | 24 | 0.033 |

Data are presented as percentages, median (interquartile range), or mean ± standard deviation. AER, albumin excretion rate. *Compared with nonalbuminuric CKD.
The prevalence of normoalbuminuria was 16% in patients with CKD. This is in line with two smaller studies that explored the relationship between albuminuria and CKD development over time in patients with type 1 diabetes. In these studies, which varied in methodology, nonalbuminuric CKD was observed in 7 and 24% of patients with new-onset CKD (18,19). The prevalence is significantly lower than in patients with type 2 diabetes, in whom the prevalence varies between 35 and 57% in follow-up studies (6–9) and between 51 and 70% in follow-up studies (14,25). The lower prevalence and incidence of nonalbuminuric CKD in type 1 diabetes could at least partially be explained by the lower age of the patients.

In the current study, nonalbuminuric CKD did not increase the risk of albuminuria or ESRD compared with nonalbuminuric non-CKD. The small number of patients with nonalbuminuric CKD would, of course, reduce the power to detect a positive association if the effect size is small. The risk of both albuminuria and ESRD was, however, of the same magnitude in patients without albuminuria with and without CKD, and adjustment for the large age difference in these groups and for other confounders did not alter the results. Patients with albuminuria, however, had a markedly increased risk of ESRD, which was 33-fold in those without baseline CKD and 221-fold in those with baseline CKD. It is of note that 370 of 378 patients that developed ESRD had albuminuria at baseline. In patients with type 2 diabetes, nonalbuminuric CKD has been shown to increase the risk of renal outcomes in some studies (5) but not in others (16,26). The discrepancy can partially be explained by differences in patient characteristics and study designs.

In our study, nonalbuminuric CKD was associated with a twofold increased risk of incident cardiovascular events during follow-up. This risk was of the same magnitude as in patients with albuminuric non-CKD but lower than in those with albuminuric CKD (threefold). A similar pattern was observed for all-cause mortality, with a twofold increased risk related to nonalbuminuric CKD, threefold risk related to albuminuric non-CKD, and eightfold risk related to albuminuric CKD. In patients with type 2 diabetes, similar findings have been observed for the risk of cardiovascular outcomes (5,16) and for all-cause mortality (1). The study population in the latter study was significantly older than ours, and thus, the 10-year survival was also poorer.

The strengths of this study are that the large study population is fairly representative of patients with type 1 diabetes in Finland and that we have a long follow-up of 13 years, and thus, also a significant number of end points were studied. The albuminuria status at baseline was well characterized; however, the eGFR was estimated from a single creatinine measurement. Thus, some of the patients with nonalbuminuric CKD may transiently have had reduced eGFR values and not have had persistent CKD. The age at onset age limit of 40
Boehringer Ingelheim, Cebix, Medscape, and Novartis. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** L.M.T. designed the study, contributed to acquisition of data, researched data, and wrote the manuscript. D.G., V.H., S.H., R.M., M.S., N.T., and J.W. contributed to acquisition of data, revision of the manuscript. P.-H.G. contributed to study design, acquisition of data, revision of the manuscript, and coordination of the study. C.M.F. designed the study, contributed to acquisition of data, researched data, and contributed to aspects of the manuscript. P.-H.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** An abstract of this work was presented at the 28th Annual General Meeting of the European Diabetic Nephropathy Study Group, Gentofte, Denmark, 23–23 May 2015.

**References**