Chronic kidney disease and mortality risk among older patients with type 2 diabetes mellitus (ZODIAC-24)

IEFKE DRION1, KORNELIS J. VAN HATEREN1, HANNEKE JOOSTEN2, ALAA ALKHALAF1,3, KLAAS H. GROENIER1,4, NANNIE KLEEFSTRA1,5,6, JACK F. M. WETZELS7, HENK J. G. BIL01,3,6

1Diabetes Centre, Isala Clinics, PO Box 10400 8000 GK Zwolle, Overijssel 8000 GK, The Netherlands 2Department of Nephrology, University Medical Centre Groningen, Groningen, The Netherlands 3Department of Internal Medicine, Isala Clinics, Zwolle, The Netherlands 4Department of General Practice, University Medical Center Groningen, Groningen, The Netherlands 5Langerhans Medical Research Group, The Netherlands 6Department of Internal Medicine, University Medical Center Groningen, Groningen, The Netherlands 7Department of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Address correspondence to: I. Drion. Tel: (+31) 38 4247942; Fax: (+31) 384243367. Email: i.drion@isala.nl

Abstract

Objective: to investigate the association between a decreased estimated glomerular filtration rate (eGFR), albuminuria and mortality in elderly patients with type 2 diabetes mellitus (T2DM).

Design: prospective observational cohort study.

Setting: primary care.

Subjects: eight hundred and ten patients, ≥65 years with T2DM. Analyses were performed in age strata: 65–75 (n = 471), >75 (n = 339) years.

Methods: Cox proportional hazard modelling was used to investigate the association between eGFR, albuminuria and all-cause and cardiovascular mortality after a median follow-up of 9.8 years.

Results: an eGFR <45 and 45–60 ml/min/1.73 m2 is associated with increased cardiovascular mortality in patients of 65–75 years, hazard ratio (HR): 3.29 (1.58–6.86) and 1.78 (1.09–2.90), respectively; in those >75 years increased cardiovascular mortality was observed when eGFR was <45 ml/min/1.73 m2: 2.42 (1.47–3.69). Compared with patients of 65–75 years, an eGFR >60 ml/min/1.73 m2 and normo-albuminuria, fully adjusted HRs for cardiovascular mortality were 2.26 (1.04–4.92) and 4.86 (2.33–10.15) for those aged 65–75 years, an eGFR of 45–60 ml/min/1.73 m2 and normo-albuminuria or albuminuria, respectively; HRs were 1.33 (0.67–2.66) and 2.01 (1.02–3.94), respectively, for those >75 years.

Conclusions: an eGFR of 45–60 ml/min/1.73 m2 in T2DM patients is associated with increased mortality in patients aged 65–75 years but not in those >75 years. Albuminuria is associated with increased mortality in patients >65 years.

Keywords: chronic kidney disease, albuminuria, diabetes mellitus, renal function, elderly

Introduction

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease, cardiovascular mortality as well as all-cause mortality [1–3]. As a consequence, there has been increasing focus on the prevention and early detection of CKD. Some of the present CKD guidelines recommend follow-up and treatment when the estimated glomerular filtration rate (eGFR) falls below 60 ml/min/1.73 m2 [4]. However, a substantial part of the older population has an eGFR <60 ml/min/1.73 m2. The clinical significance of moderate reductions of eGFR in older people is still debated [5–7]. Some argue that in the absence of other abnormalities, an
age-related decrease in eGFR is physiological; others state that a reduction in eGFR in individuals >65 years may reflect the high prevalence of kidney disease risk factors at older age [8]. In spite of the uncertainties regarding clinical significance, follow-up of renal function is indicated, since older patients can also have an underlying renal disease or factors adding to the progression of kidney disease.

The number of older people with type 2 diabetes mellitus (T2DM) is increasing thanks to earlier diagnosis and better survival. Therefore, complications, such as diabetic nephropathy, occur more frequently [9] and screening for kidney disease has become a cornerstone of diabetes care [10]. However, the association between eGFR, albuminuria and mortality has been sparsely investigated in older diabetic patients [11]. Moreover, classic cardiovascular risk factors seem to have a diminished effect when assessed in patients >75 years [12, 13]. Therefore, we aimed to investigate the association between eGFR, albuminuria and mortality in older patients with T2DM, stratified according to age (65–75 years and >75 years).

**Methods**

In 1998, the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study was initiated in the Zwolle region, the Netherlands. The design and details of this study have been presented elsewhere [14]. Briefly, the ZODIAC study is part of a shared care project, in which general practitioners are assisted by hospital-based nurses specialised in their care of patients with T2DM. At baseline, patients being treated by a specialist of internal medicine (20%) or patients with a very short-life expectancy (including patients with active cancer) or insufficient cognitive abilities as judged by the general practitioner were excluded. Ultimately, general practitioners excluded 5% of the patients treated in primary care for T2DM.

Approximately 90% (n = 1,357) agreed to participate; four patients were excluded because of insufficient baseline data. For the present study, we selected all patients ≥65 years with complete information on all confounders (n = 810). The ZODIAC study was approved by the medical ethics committee, and all patients provided informed consent.

**Data collection**

Baseline data were collected from 1998 to 1999 and consisted of a full medical history including assessment of macrovascular complications, medication use, diabetes duration and tobacco consumption. Macrovascular complications were defined as a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack. Laboratory and physical assessment data were collected annually and included glycated haemoglobin (HbA1c), non-fasting lipid profile, plasma creatinine (a kinetic colourimetric Jaffé method was used (Modular P Analyzer, Roche Almere, the Netherlands), albumin-to-creatinine ratio [ACR, assessed in a spot morning urine sample using immunonephelometry (Behring Nephelometer; Mannheim, Germany)], blood pressure (measured twice with a Welch Allyn sphygmomanometer), bodyweight and height.

Rental function was estimated by the Modification of Diet in Renal Disease equation (MDRD) [15]. MDRD was categorised into three classes: <45, 45–60 and ≥60 ml/min/1.73 m2. Albuminuria was defined as an ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women. The overall cohort (n = 810) was divided into a low- (65–75 years, n = 471) and a high-age group (>75 years, n = 339).

**Clinical endpoints**

Two clinical endpoints were examined: all-cause and cardiovascular mortality. In 2009, the vital status and cause of death were retrieved from records maintained by the hospital and general practitioners.

**Statistical analyses**

SPSS version 16.0 (SAS Institute, Cary, NC, USA) and STATA version 11.0 (Stata Corp., College Station, TX, USA) were used for statistical analyses.

A Cox proportional hazard model was used to investigate the association between eGFR, ACR and mortality with adjustment for selected confounders. The associations were investigated for the eGFR as a categorical variable as well as a continuous variable (using baseline MDRD values) and for albuminuria as a categorical variable. Hazard ratios (HRs) for covariates were calculated for changes in eGFR of 10 ml/min/1.73 m2.

The following possible confounders were selected: age, gender, smoking (dichotomous), body mass index, systolic blood pressure, history of macrovascular complications (dichotomous), diabetes duration, HbA1c, use of carbasalate calcium, use of lipid lowering medications, the total cholesterol–HDL ratio and albuminuria (dichotomous), the eGFR was added and albuminuria was removed as a confounder when the association between normo-albuminuria and mortality was tested.

Three different models were analysed: model 1 (crude), model 2 (including all selected confounders) and model 3 in which all selected confounders were used, except variables that were already used in the MDRD (sex and age). The latter model was performed to reduce the phenomenon of multi-collinearity and to evaluate the influence of omitting these variables on the association between renal function predicted by the MDRD and mortality.

Cox regression analyses were performed to investigate the association of albuminuria with all-cause and cardiovascular mortality; these analyses were repeated in eGFR categories ≤ and >60 ml/min/1.73 m2 with and without albuminuria. Since stratification by the level of ACR may be
warranted in terms of association with mortality, we tested the interaction between the MDRD (as continuous and as categorical variable) and the ACR.

For Kaplan–Meier curves, eGFR baseline values were categorised into three different groups: <45, 45–60 and >60 ml/min/1.73 m².

Results

Baseline characteristics of the population are shown in Table 1. Patients >75 years had an eGFR <60 ml/min/1.73 m² (n = 213; 63%) and albuminuria (n = 176; 52%) more frequently than patients aged 65–75 years (n = 195; 41% and n = 209; 44%, respectively).

Two hundred and seventy-four patients (81%) in the high-age group and 170 patients (36%) in the low-age group died after a follow-up time of 10 years. In 27 patients (3%), the cause of death was unknown, 19 patients were lost to follow-up. The proportion of deaths attributable to cardiovascular causes was 43% in the high-age group and 42% in the low-age group.

Renal function estimates and plasma creatinine

Table 2 (for Table 3, please see the Appendix 1 in the Supplementary data available in Age and Ageing online) presents the HRs for cardiovascular and all-cause mortality for eGFR categories and normo-albuminuria. The MDRD as a continuous variable was associated with both increased all-cause as well as cardiovascular mortality in all models of both age groups. After adjusting for confounders, the cardiovascular mortality risk increased by 64% [95% confidence interval (95% CI): 33–96%] and 47% [95% CI: 25–75%] for every 10 ml/min/1.73 m² decrease.
in eGFR in the low- and high-age group, respectively (model 3).

Patients with an eGFR <45 ml/min/1.73 m² in the high-age group had an increased risk for all-cause and cardiovascular mortality compared with the reference category (>60 ml/min/1.73 m²). Such a relationship was not observed for eGFR values between 45 and 60 ml/min/1.73 m². In contrast in patients aged 65–75 years, cardiovascular mortality risk was increased in patients with eGFR values between 45 and 60 ml/min/1.73 m². The HRs of model 1 and 2 for all-cause mortality in this age group were not significant for patients with an eGFR <60 ml/min/1.73 m². However, the results of model 3 show that the risk of all-cause mortality was increased for patients with an eGFR value below 60 ml/min/1.73 m² compared with higher levels. Figure 1 shows the association between eGFR, and cardiovascular mortality in both the low- (Figure 1A) and the high (Figure 1B)-age group (for all-cause mortality please see the figure Appendix 2 in the Supplementary data available in Age and Ageing online).

### Discussion

In this study, renal function loss was related to both increased all-cause and cardiovascular mortality. In patients >75 years, increased all-cause and cardiovascular mortality was only observed when the eGFR was <45 ml/min/1.73 m², this in contrast to elderly patients aged 65–75 years in which an increased risk for cardiovascular mortality was observed when renal function estimates dropped below 60 ml/min/1.73 m². Albuminuria was independently associated with all-cause and cardiovascular mortality irrespective of eGFR in both age groups. The fact that in model 3 the risk of all-cause mortality was increased for patients with an eGFR value <60 ml/min/1.73 m² compared with higher levels, shows that multi-collinearity occurs when age and sex are, next to its presence in the MDRD formula, also used as a confounder (such as in model 2).

Thus, age seems to be an important effect modifier in CKD. A meta-analysis in general population cohorts showed independent and joint associations of albuminuria and eGFR <60 ml/min/1.73 m² on cardiovascular and all-cause mortality [16]. However, the number of patients >70 years was relatively small and associations were not evaluated in separate age cohorts. Other studies investigating the consequences of a reduced eGFR in patients >75 years in the general population have shown that if normo-albuminuric, mortality risk is only increased when eGFR is <45 ml/min/1.73 m² [17–19]. Moreover, older patients had higher rates of death and lower rates of end-stage renal disease than younger patients at comparable levels of eGFR [20]. From a cross-sectional study in older people, it appeared that an eGFR <45 ml/min/1.73 m² mainly identifies a smaller sub-group of people >75 years with significant comorbidity, impaired functional state and a high risk of potentially reversible consequences (e.g. anaemia) [21].

Most of the above-mentioned studies contained only few diabetes patients or patients >75 years. A study...
among diabetic patients >65 years showed that albuminuria and an eGFR <60 ml/min/1.73 m² were independent risk factors for mortality [2]. However, the observed relationship might have been largely attributable to the proportion of patients with an eGFR <45 ml/min/1.73 m². Our results show that even in normo-albuminuric patients with T2DM, >75 years, an eGFR of 45–60 ml/min/1.73 m² is not associated with an increased risk for cardiovascular and all-cause mortality, in contrast to those aged 65–75 years. Our results are confirmed by a recent meta-analysis in normo-albuminuric patients at high risk for CKD (n = 106 690, 40% had diabetes), whose risk for all-cause mortality was increased at eGFR levels <60 ml/min/1.73 m² [3]. However, in subjects ≥65 years, significance was reached at a lower level (<45 ml/min/1.73 m²), as opposed to subjects <65 years. No specific analyses were made for patients >75 years.

The attenuation of the association of mortality with certain eGFR stages in older patients as we observed; was not found for albuminuria. This is confirmatory with previous studies. An independent association between proteinuria and mortality has been shown in patients with and without diabetes. In the HUNT II study, the presence of micro-albuminuria or high-normal ACR ratios was associated with increased cardiovascular mortality below the threshold of 75 ml/min/1.73 m² compared with those with normo-albuminuria [18]. A more recent study found in a largely male cohort that the ACR in diabetes patients >65 years was independently associated with mortality at all levels of eGFR [11]; an observation that is in agreement with our study. In contrast to our study, a large study in primary care, investigating the association between dipstick proteinuria, eGFR and mortality in patients aged >75 years, the presence of dipstick proteinuria did not add to cardiovascular mortality risk. This is remarkable since one would expect that especially when a dipstick is used, the risk of cardiovascular mortality would have been higher [19]. Also another study in older individuals referring patients with CKD stage 4 did not find a statistically significant association between level of proteinuria and risk of death; 33% was >75 years) [22]. An explanation for the discrepancy in the two last mentioned studies and our study results has not been found.

The absence of an association of moderate reduction in eGFR with mortality at older age may have been caused by the fact that the MDRD was not developed for use in older patients. Moreover, creatinine is a poor marker of renal function in these patients leading to inaccuracy [23, 24]. Secondly, older patients have higher background mortality and a higher prevalence of comorbidity [25]. Finally moderate reductions in eGFR may reflect a physiological decline in renal function with advancing age [26, 27]. Since albuminuria reflects another pathway of kidney damage than eGFR, this may explain we found no attenuation of the association between albuminuria and increased cardiovascular mortality [28, 29].

**Strengths and limitations**

Our study has some methodological aspects that need discussion. First, our study cohort is rather small, especially the group with an eGFR <45 ml/min/1.73 m². Therefore, the results should be interpreted with caution. Owing to the small numbers no differentiation in micro- and macro-albuminuria was made since the number of patients in the separate groups would become too small. Second, we have used uncalibrated plasma creatinine measurements. This might have induced systematic errors in eGFR values. Fortunately, all creatinine measurements were performed in the same laboratory, so interlaboratory variation was excluded. Selection bias may have occurred, since patients with a short-life expectancy and patients treated in hospital for their diabetes were excluded. Finally, the MDRD has not been validated in patients >70 years. Strengths are the prospective nature, the possibility to take into account many possible confounders with few missing data, and the long follow-up.

In conclusion, patients >75 years with T2DM and an eGFR of 45–60 ml/min/1.73 m² are not at increased risk for all-cause and cardiovascular mortality compared with their counterparts with an eGFR >60 ml/min/1.73 m². In contrast, albuminuria at all levels of eGFR is strongly associated with increased all-cause and cardiovascular mortality, and therefore may have potential as a more discriminative risk stratification tool in the large group of older patients with moderate reductions in eGFR (45–60 ml/min/1.73 m²). In this study, as in most studies of CKD in older individuals, patients with moderate decrements of renal function account for a large proportion of the older population with CKD, which suggests that the current staging system, taking into account eGFR only, may not be a reliable tool for older patients, at least when used to assess increased cardiovascular risk.

**Key points**

- Patients with moderate decrements of renal function account for a large proportion of the elderly population with CKD.
- An eGFR of 45–60 ml/min/1.73 m² in patients >75 years with T2DM is not associated with an increased mortality risk.
- Albuminuria at all levels of eGFR is strongly associated with increased all-cause and cardiovascular mortality.
- The current staging system for CKD may not be a reliable tool for cardiovascular risk stratification in elderly patients.

**Conflicts of interest**

None declared.
Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References


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