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Risk factors for decline in renal function among young adults with type 1 diabetes

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Abstract

Aims: To investigate risk factors for declining renal function among subjects with type-1-diabetes.

Methods: Observational study based on data from the diabetes registry DPV. 4,424 type-1-diabetes subjects aged ≥18 years, age at onset <18 years were identified. Modification of Diet in Renal Disease (MDRD) equation was used to estimate glomerular filtration rate (eGFR). Annual rate of renal decline was estimated for each patient using hierarchic linear regression models. Additional regression models were fitted to adjust for covariates.

Results: Median age was 26 [Q1; Q3: 21; 39] years. Annual decline of renal function was -1.22 (95% CI: -1.50; -0.94) ml/min/1.73m^2. At baseline, higher eGFR was related to more rapid decline compared to impaired or reduced eGFR (GFR≥90: -2.06 (-2.35; -1.76), 60≤GFR<90: 0.45 (0.08; 0.81), GFR<60: 0.52 (-0.24; 1.29) ml/min/1.73m^2, p<0.01). During follow-up, highest decline was associated with reduced renal function, whereas lowest decline was related to normal kidney function (p<0.01). Poor metabolic control (p=0.04), hypertension (p<0.01) and albuminuria (p=0.03) were associated with more rapid loss of kidney function. No difference was observed among insulin regimen.

Conclusion: Among this large type-1-diabetes cohort, more rapid loss of kidney function was related to higher baseline eGFR, log-term worse metabolic control and diabetic comorbidities.

Keywords: Type-1-Diabetes; kidney function; renal decline

1. Introduction

The progressive loss of renal function over a long time-period is described as chronic kidney disease (CKD), reflected by a decline in glomerular filtration rate (GFR) (1). The risk for reduced renal function is higher among subjects with diabetes compared to the general population. Diabetes is the most common cause of kidney disease leading to multiple complications and progression to end-stage renal disease (ESRD) (2,3). Although efforts in treating type-1-diabetes have resulted in better prognosis, 30-40 % of these subjects are affected by nephropathy in long-term follow-up (4,5).

CKD is a growing world-wide public health concern (6). Over the past two decades an increasing prevalence of reduced GFR was found (7). Reduced renal function is a marker for worse outcome, reduced quality of life, and decreased life expectancy (8-10). With longer diabetes duration, the majority is affected by impaired renal function (5). In a Norwegian type-1-diabetes cohort diagnosed at age 15 to 29 years, time from onset of diabetes to ESRD was 23.6 (range 14.2-33.5) years (11). A previous study revealed a graded relationship between both the presence and the severity of kidney damage and all-cause mortality (12). Although in a recent study analysing individuals with type-1-diabetes from the Swedish National Diabetes Register a decline in all-cause mortality was found (10), this data still showed that mortality was higher with impaired kidney function or severe renal complications (including albuminuria and CKD) (13).

The pathogenesis of diabetic kidney disease is multifactorial. Albuminuria, advancing age, worse metabolic control, cardiovascular complications, increased blood pressure and body mass index (BMI), smoking as well as genetic/ethnic factors might contribute to onset and progression of kidney damage (2,14). A recent meta-analysis stated that doubling of serum creatinine corresponds to a 57% decline of kidney function and is related to a 30-fold higher risk of ESRD (6).

Nephropathy is one of the leading complications in adults with diabetes; however, its prediction remains a challenge (15). Although several previous studies analysing renal failure either among a diabetic cohort or in individuals with type-2-diabetes (8,14,16), research of young adults with type-1-diabetes is less frequent. Since a better understanding of the progression and response to early intervention may enable more targeted treatment (8), the objective of this study was to examine both baseline predictors of decline in renal function and risk factors during follow-up among a large cohort of young adults with type-1-diabetes from the multicentre diabetes registry DPV.

2. Subjects, Materials and Methods

2.1. Data source and subjects

Patients included in this study were identified from the prospective, multicentre diabetes follow-up registry "Diabetes-Patienten-Verlaufsdokumentation" (DPV) at Ulm University, Germany. Currently, more than 450 diabetes centres in Germany, Austria, Switzerland, and Luxembourg routinely document treatment and outcome of diabetes care using the standardized DPV electronic health record. Semiannually, data stored locally are transmitted anonymously to Ulm University. After plausibility checks/corrections, data are combined into a cumulative database. Local benchmarking and scientific analyses are conducted. The analysis of anonymized data was approved by the Ethics Committee of Ulm University, Germany (4).

By March 2017, 465,977 patients were enrolled in the DPV database. Individuals were eligible for inclusion in this study if they are affected by type-1-diabetes and ≥18 years of age with age

at onset <18 years. For each patient, a minimum of three values of estimated GFR (eGFR) was mandatory. Exclusion criteria were renal dialysis or transplantation. The final study cohort comprised 4,424 adult individuals with type-1-diabetes (Figure 1). Covariates were analysed at baseline to predict renal decline and during follow-up to investigate risk factors for loss of kidney function.

2.2. Outcomes

As described previously (4), the Modification of Diet in Renal Disease (MDRD) provides a clinically useful estimate of kidney function among adults with diabetes, and was therefore used to determine GFR. GFR (ml/min/1.73m^2) was estimated as follows (17): eGFR = 175 × creatinine (mg/dl)$^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 (if female). In an alternative analysis, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate GFR (4). Sociodemographic characteristics (sex, age, duration of diabetes, migration background), clinical data (serum creatinine, diabetes therapy, haemoglobin A1c (HbA1c), self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM) or fasting glucose monitoring (FGM), BMI), and self-reported lifestyle factors (physical activity (yes/no), smoking (yes/no)) were examined. Migration background was defined if either patient and/or at least on parent were not born in Germany/Austria. Serum creatinine was expressed in mg/dl. Diabetes therapy was defined as pump therapy, intensified conventional therapy (ICT, 4-8 injection time points per day), and conventional therapy (CT, 1-3 injection time points per day). HbA1c was mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range (4.05-6.05 %, 20.7-42.6 mmol/mol) by applying the multiple-of-the-mean transformation method (18). The number of SMBG was assessed during patient contacts. CGM/FGM usage was derived from a separate entry in the DPV software. BMI was calculated as kg/m^2. At least one episode of physical activity of at least 45 min per week was defined as being physically active. At least one cigarette per day was defined as smoking.

Renal function was grouped into normal (≥90 ml/min/1.73m^2), impaired (60-<90 ml/min/1.73m^2), and reduced eGFR (<60 ml/min/1.73m^2). Nephropathy was classified as albuminuria (urinary albumin excretion >30 mg/l). Moreover, mild albuminuria (urinary albumin excretion >20–200 mg/l) and severe albuminuria (>200 mg/l) were examined. Treatment with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARB) was evaluated. Hypertension was defined as increased systolic (≥140 mm Hg) and/or diastolic (≥90 mm Hg) arterial blood pressure or the use of antihypertensive drugs. Dyslipidaemia was defined by at least one elevated value of total cholesterol (≥200 mg/dL), LDL cholesterol (≥100 mg/dL), triglycerides (fasting ≥150 mg/dL, not fasting ≥500 mg/dL) and/or decreased levels of HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women) or by the use of lipid-lowering drugs (19). Retinopathy (proliferative or non-proliferative) was diagnosed if patients had at least one abnormal retinal examination. The proportion of patients with cardiovascular complications including a history of myocardial infarction, stroke, or peripheral vascular disease (PVD) was evaluated.

2.3. Statistical analysis

Descriptive data were summarized using median with quartiles for continuous variables or proportion for binary variables.

Due to the multicentre structure of this study, centre was entered as a random effect in the regression models to account for variation among treatment centres. As previous research

demonstrated that annual renal decline is mainly linear among type-1-diabetes cohorts (20,21), hierarchic linear regression models were applied to estimate annual loss of kidney function. For each subject, change of renal function over time was estimated weighted by number of GFR measurements (16).

Subsequently, to analyse differences in the decline of kidney function among the study cohort, multiple hierarchic linear regression models weighted by number of GFR measurements were fitted. Basically, models were adjusted for gender, age, duration of diabetes, migration background, and baseline GFR (model 1). Further potential covariates were examined by constructing multivariable models including insulin therapy, metabolic control, SMBG, BMI, diabetic comorbidities, ACE inhibitors/ARB treatment, and smoking (model 2). Risk factors for kidney decline were analysed at baseline and during follow-up. Results of regression models were presented as adjusted estimates (LSmeans with confidence intervals (95% CI)).

All two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed using Statistical Analysis Software 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The study sample comprised 4,424 adults (≥18 years) with type-1-diabetes. 50% of subjects were male. Median age was 26 [Q1; Q3: 21; 39] years with duration of diabetes 18 [11; 30] years. Serum creatinine was 0.8 [0.7; 1.0] mg/dl and baseline eGFR was 97 [83; 114] ml/min/1.73m^2.

3.1. Annual decline of renal function

Among the study cohort, annual decline of kidney function was -1.22 (95% CI: -1.50; -0.94) ml/min/1.73m^2. Analysing individuals aged >60 years separately (n=157), loss of renal function was -2.71 (-9.13; 3.72) ml/min/1.73m^2 per year. In males more rapid decline of kidney function was observed compared to females (-1.33 (-1.64; -1.02) vs -0.97 (-1.28; -0.66), p=0.01). No difference was observed for subjects with or without migration background.

3.2. Baseline risk factors for renal decline

Yearly renal decline adjusted for demographics (model 1) is shown separately for baseline comorbidities and clinical parameters in Table 1.

At baseline, higher eGFR values (≥90 ml /min/1.73m^2) were related to more rapid decline in renal function compared to impaired (60-<90 ml/min/1.73m^2) or reduced (<60 ml/min/1.73m^2) eGFR (p<0.01). In subjects affected by albuminuria at baseline, loss of renal function was more rapid compared to individuals without albuminuria (p=0.02). Highest decline was observed among patients with severe albuminuria (p=0.04). Among patients treated with ACE inhibitors/ARB at baseline, higher rate of renal decline was found (p=0.03).

Diabetes comorbidities at baseline tended to predict more rapid renal decline. Baseline metabolic control, insulin regime, SMBG, sensor usage as well as lifestyle factors were not associated with renal decline. Similar results were found in model 2 (data not shown).

3.3. Risk factors for loss of kidney function during follow-up

In this study cohort, median observation period was 4 [3; 8] years. In Table 2, rate of renal decline adjusted for both demographics (model 1) and for demographics and additional covariates (model 2) are shown separately for diabetic comorbidities and clinical parameters.

Highest decline was observed among patients with reduced renal function (GFR<60 ml/min/1.73m^2), whereas lowest decline was found in subjects with a normal kidney function (GFR≥90 ml/min/1.73m^2). Albuminuria was associated with higher kidney decline (p=0.02). Rapid kidney decline was more likely among subjects with mild albuminuria (p<0.01) or severe albuminuria (p<0.01). In patients treated with ACE inhibitors/ARB, loss of renal function tended to be more rapid. These findings remained significant even after adjusting for additional covariates.

In individuals with hypertension, annual rate of kidney decline was higher compared to those without hypertension in the basic model (p<0.01) and in model 2 (p<0.01). In subjects with impaired kidney function and hypertension, renal decline was accelerated (-2.06 (-2.51; -1.62) ml/min/1.73m^2) compared to subjects without hypertension (-1.79 (-2.26; -1.34) ml/min/1.73m^2). Cardiovascular complications were related to more rapid kidney decline (p=0.03), even after adjusting for further covariates.

Long-term worse metabolic control was associated with more rapid kidney decline (p<0.01). Lowest decline was found among patients with good metabolic control (HbA1c <58 mmol/mol) whereas HbA1c ≥75 mmol/mol was related to the highest decline. Even after adjustment for further covariates, similar findings were found. Figure 2A depicts annual rate of kidney decline separated by GFR groups and HbA1c levels. With increasing HbA1c, accelerated loss of kidney function was observed among individuals with impaired or reduced renal function. Most rapid decline was found among subjects with both reduced renal function (GFR<60 ml/min/1.73m^2) and HbA1c ≥75 mmol/mol (-6.43 (-7.99; -4.86) ml/min/1.73m^2).

Similar loss of filtration rate was found among therapy regimes in the basic model and in model 2. Figure 2B shows the interaction between kidney decline and both diabetes therapy and metabolic control. Among insulin pump users, higher HbA1c was related to more rapid renal decline (p<0.01). However, in individuals treated with CT or ICT decline was similar across HbA1c levels. No difference was found for CGM/FGM usage in both the basic model and in model 2.

3.4. Analysis based on CKD-EPI equation

In this alternative analysis, the CKD-EPI equation was used to estimate GFR. Yearly decline of kidney function was -1.07 (-1.32; -0.81) ml/min/1.73m^2. Analysing individuals aged >60 years, loss of renal function was -2.50 (-8.67; 3.67) ml/min/1.73m^2. Results of kidney decline separated by comorbidities, diabetes therapy and clinical parameters at baseline and during follow-up are shown in the Supplementary Table 1.

At baseline similar findings were observed for the CKD-EPI estimated loss of renal function compared to the MDRD estimations, except for cardiovascular complications and retinopathy. Cardiovascular complications and retinopathy were related to higher renal decline.

Compared to the MDRD estimations, no clinically relevant differences were found during follow-up with the CKD-EPI equation, except for cardiovascular complications and HbA1c groups. Even after adjustment for demographics and additional covariates (model 2), higher loss of renal function was found in patients with cardiovascular events. No significant difference was found among HbA1c groups after adjusting for covariates (model 2).

4. Discussion

This large observational study based on data from the DPV registry demonstrates that decline of kidney function varies in young adults with type-1-diabetes depending on metabolic control, GFR levels at study onset, and diabetic comorbidities. At baseline, higher eGFR values (≥90 ml/min/1.73m^2) were related to more rapid decline in renal function compared to impaired or reduced eGFR. More rapid loss of kidney function was associated with long-term worse metabolic control as well as albuminuria and hypertension. However, no significant difference was observed across insulin regimes.

Age-dependent yearly renal decline of 0.75-1.00 ml/min/1.73m^2 is described as normal in healthy subjects (15,22). However, functional deterioration of the kidney varies widely among individuals depending on several factors such as age, gender, ethnicity or underlying conditions. Even though a large body of evidence stated that either elderly individuals with diabetes (8,16) or subjects with type-2-diabetes (14) experience more rapid loss of renal function, reports of young adults with type-1-diabetes are less frequent. In accordance with a previous research in a small type-1-diabetes cohort (23), we revealed an annual renal decline of -1.22 (-1.50; -0.94) ml/min/1.73m^2 among young adults with type-1-diabetes. As the kidney also undergoes age-dependent changes (24), Hemmelgarn and colleagues investigated progression of kidney damage in a large cohort of elderly subjects with diabetes (8). In line with our findings of higher loss of renal function among elderlies, the authors reported a decline of 2.7 and 2.1 ml/min/1.73m^2 in males and females, respectively.

Previous studies demonstrated that higher baseline eGFR predicts greater odds of rapid functional deterioration of the kidney (23,25). A previous study stated that early rapid kidney decline was associated with both high baseline GFR and prevalence of albuminuria (15). In a small cohort of type-1-diabetes patients, an increase in the odds of early renal function decline was found for every 10 ml/min/1.73 m^2 increase in baseline kidney function (15). The mechanism initiating rapid renal decline remains controversial. Due to diabetes-related comorbidities, renal arteriolar as well as glomerular function and structural defects might be included (15). Furthermore, previous studies reported an association between hyperfiltration and early kidney function decline (15).

In contrary, highest decline was observed during follow-up among subjects with reduced kidney function, whereas lowest decline was found in subjects with a normal renal function. Several studies have demonstrated increasing progression of kidney damage over time with decreasing GFR levels (8,25). A previous research analysing percentage change of GFR corroborated our finding that rapid decline was more likely to occur among those with reduced renal function (GFR <60 ml/min/1.73m^2, 33.8%) compared to those with impaired (60-<90 ml/min/1.73m^2, 11.9%) or normal kidney function (≥90ml/min/1.73m^2, 9.9%) (26). Moreover, rapid loss of renal function over time has been identified as a risk factor for ESRD and mortality (6,27). The risk of death increased from 4 times in individuals with GFR >120 ml/min/1.73 m^2 to 30 times in subjects with GFR <15 ml/min/1.73 m^2 compared to non-diabetic controls (27).

Elevated HbA1c level as a marker of chronic hyperglycaemia might be the most established risk factor for nephropathy (3,15,28). A previous study pointed out that not poor baseline but worse long-term metabolic control increases the risk of functional deterioration of the kidney

(23). For every 1% increase in HbA1c a 16% increase in albuminuria was found previously (9). Larger variability of HbA1c predicts development and progression of diabetic kidney disease (29,30).

While the DCCT/EDIC Research group exhibited a lower long-term risk for impaired kidney function in a type-1-diabetes cohort treated with ICT compared to CT (3), similar loss of renal function for all therapeutic regimes was found in the present study. In a recent study analysing the risk of CKD, reduced renal function as well as albuminuria, no significant association with insulin therapy was observed at baseline and during follow-up (9). A Swedish study investigating long-term effects of insulin pump therapy exhibited that despite similar HbA1c, patients treated with insulin pump were younger with less albuminuria and renal insufficiency compared to subjects treated with injections therapy (31). Among insulin pump users with long-term poor metabolic control, higher loss of kidney function was found, while in individuals with injection therapy no significant interaction between HbA1c levels could be observed. Different findings might be due to heterogeneous study cohorts, analysing a dichotomous outcome or percent change of loss of kidney function or different methods to estimate GFR.

With increasing HbA1c levels, we observed more rapid loss of kidney function among individuals with GFR <90 ml/min/1.73 m^2 and the most rapid decline was found among subjects with both <60 ml/min/1.73m^2 and HbA1c ≥9 %. Lind and colleagues suggested to assess diabetic kidney disease as a mediator of the link between worse metabolic control and adverse outcome rather than as an independent risk factor of HbA1c (27). As nephropathy may be prevented by keeping HbA1c in target range (28,32), health care professionals and patients should focus on appropriate and preventive interventions to improve metabolic control.

In clinical practice albuminuria is used as a primary determinant of renal damage and may be a main predictor of both early nephropathy and progression of CKD (12,33). In the current study, functional deterioration of the kidney was more likely to occur among individuals with albuminuria at baseline and during follow-up than in those without albuminuria. Previous studies reported a graded association of albuminuria and renal decline (12,34) and demonstrated an increased risk of progression to kidney failure and death in individuals with high levels of proteinuria (34). Costacou and Orchard (5) reported that more than half of type-1-diabetes adults are affected by microalbuminuria after 20 years of diabetes duration and 27% by macroalbuminuria. The FinnDiane Study Group stated that mortality rate of individuals with macroalbuminuria was over nine times and with microalbuminuria over twice higher compared to the general population (12).

Hypertension is another well-known risk factor for the development and progression of CKD. Several previous studies exhibited an association between elevated blood pressure levels and diabetic nephropathy (2,28). In this research, baseline hypertension did not predict renal decline, whereas continuous high blood pressure during follow-up might be a promoter of rapid loss of kidney function. In a recent review, the authors stated that individuals with lower blood pressure and renal disease experience slower disease progression compared to renal patients with comorbid hypertension (35). Young et al (26) demonstrated that individuals with GFR <60 ml/min/1.73m^2 were more likely to be affected by hypertension compared to those with higher levels of GFR. Since high blood pressure can be described either as a cause or a consequence of diabetic kidney disease (26), hypertension should be treated strictly.

The Kidney Disease Outcomes Quality Initiative (K/DOQI) and the American Diabetes Association (ADA) recommend ACE inhibitors and ARBs as preferred treatment for diabetic kidney disease to reduce proteinuria, slow the progression of kidney disease, and lower blood pressure (36,37). *In this study, more rapid decline was observed among individuals treated with ACE inhibitors or ARB therapy at baseline; however, during follow-up no significant difference could be found in the current study.*

The present study has some limitations. Due to the multicentre structure, variability in measurements cannot be eliminated completely, although procedures are standardized by guidelines. Rates of renal function might be heterogeneous as a result of different estimation methods used to determine eGFR (38,39). In a previous study among a large diabetic cohort, we showed highest accuracy for the MDRD (4). Similar performance was observed for the MDRD and CKD-EPI in subjects with normal and impaired kidney function; however, in individuals with reduced kidney function the MDRD provided highest accuracy (4). Another limitation might be that some patients with nephropathy have nonlinear GFR patterns (1). However, several studies reported the pattern of GFR decline as predominantly linear among type-1-diabetes cohorts (20,21). Since Skupien et al (21) concluded that a linear pattern of kidney function deterioration over time carries sufficient information for reliable risk stratification, linear regression models were applied in this study. Despite these limitations, the strengths of this study are the large number of young adults with type-1-diabetes from various parts of Germany/Austria. Moreover, the standardized documentation of "real-life" clinical data allows to examine several predictors for the decline of renal function at baseline and during follow-up.

In summary, we show in an observational setting that high baseline GFR as well as long-term worse metabolic control and diabetic comorbidities are associated with more rapid renal decline in young adults with type-1-diabetes. These findings highlight the clinical importance of diabetic nephropathy and its prevention in the management of type-1-diabetes.

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Disclosures

The authors declare that they have no conflicts of interest relevant to this article.

Author Contributions

AS performed statistical analysis, interpreted results and wrote/edited the manuscript. RWH contributed to statistical analysis and interpretation of results as well as reviewed/edited the manuscript. DB, MD, KSCG, DS, HS, SZ researched data und reviewed/edited the manuscript. RWH is the principal investigator of the DPV initiative and has full access to the data. All co-authors approved the final version to be published.

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Table 1 Yearly kidney decline separated by baseline comorbidities, diabetes therapy and clinical parameters.

	Model 1	P value
Baseline diabetic comorbidities		
Stages of CKD		
GFR ≥ 90 ml/min/1.73m^2	-2.06 (-2.35; -1.76)	
60 ≤ GFR < 90 ml/min/1.73m^2	0.45 (0.08; 0.81)	<0.01
GFR < 60 ml/min/1.73m^2	0.52 (-0.24; 1.29)	
Albuminuria		
Albuminuria	-1.58 (-2.06; -1.10)	0.02
No albuminuria	-0.99 (-1.32; -0.66)	
Mild albuminuria		
Mild albuminuria	-1.79 (-2.33; -1.26)	<0.01
No mild albuminuria	-0.97 (-1.30; -0.64)	
Severe albuminuria		
Severe albuminuria	-3.04 (-4.96; -1.12)	0.04
No severe albuminuria	-0.97 (-1.30; -0.64)	
Hypertension		
Hypertension	-1.17 (-1.59; -0.74)	0.78
No hypertension	-1.11 (-1.39; -0.83)	
Cardiovascular complications		
Cardiovascular complications	-1.56 (-2.13; -0.97)	0.08
No Cardiovascular complications	-1.04 (-1.32; -0.77)	
Retinopathy		
Retinopathy	-1.34 (-1.89; -0.80)	0.06
No retinopathy	-0.76 (-1.14; -0.38)	
Dyslipidemia		
Dyslipidemia	-1.18 (-1.47; -0.88)	0.36
No dyslipidemia	-1.02 (-1.37; -0.67)	
Baseline diabetes therapy and clinical parameters		
Therapy		
Insulin pump	-1.28 (-1.69; -0.88)	
CT	-1.20 (-1.74; -0.66)	
ICT	-1.13 (-1.45; -0.81)	0.38
Metabolic control		
HbA1c ≥ 9 % (HbA1c ≥75 mmol/mol)	-1.15 (-1.56; -0.75)	
7.5 ≤ HbA1c < 9 % (58≤ HbA1c <75 mmol/mol)	-1.21 (-1.56; -0.86)	0.38
HbA1c < 7.5% (HbA1c <58 mmol/mol)	-0.99 (-1.31; -0.67)	
ACE inhibitors/ARB		
ACE inhibitors/ARB	-2.36 (-3.55; -1.18)	0.03
No ACE inhibitors/ARB	-1.07 (-1.34; -0.79)	
Self-monitoring		
SMBG < 4 per day	-0.87 (-1.31; -0.43)	
4 ≤ SMBG ≤ 6 per day	-1.23 (-1.54; -0.92)	0.09
SMBG > 6 per day	-1.37 (-2.11; -0.64)	
BMI		
BMI < 30 kg/m^2	-1.10 (-1.38; -0.82)	<0.01
BMI ≥ 30 kg/m^2	-1.97 (-2.59; -1.36)	
Physical activity		
Physical activity	-1.25 (-1.68; -0.82)	0.39
No physical activity	-1.06 (-1.35; -0.78)	
Smoking		
Smoking	-1.29 (-1.73; -0.85)	0.30
No smoking	-1.07 (-1.35; -0.80)	

Hierarchic linear regression models weighted by number of GFR measurements were fitted. Model 1 was adjusted for sex, migration background, age, duration of diabetes, and GFR at baseline.

Table 2 Kidney decline separated by comorbidities, diabetes therapy, and clinical parameters during follow-up.

	Model 1	P value	Model 2	P value
Diabetic comorbidities				
Stages of CKD				
GFR ≥ 90 ml/min/1.73m^2	-0.10 (-0.40; 0.20)		-0.17 (-0.49; 0.16)	
60 ≤ GFR < 90 ml/min/1.73m^2	-2.09 (-2.43; -1.76)	<0.01	-1.93 (-2.30; -1.58)	<0.01
GFR < 60 ml/min/1.73m^2	-5.12 (-5.73; -4.52)		-4.80 (-5.46; -4.13)	
Albuminuria				
Albuminuria	-1.32 (-1.67; -0.97)	**0.02**	-1.35 (-1.78; -0.92)	0.03
No albuminuria	-0.89 (-1.19; -0.58)		-0.86 (-1.23; -0.47)	
Mild albuminuria				
Mild albuminuria	-1.42 (-1.80; -1.03)	<0.01	-1.43 (-1.88; -0.98)	0.02
No mild albuminuria	-0.88 (-1.18; -0.58)		-0.86 (-1.25; -0.48)	
Severe albuminuria				
Severe albuminuria	-3.96 (-5.05; -2.87)	<0.01	-3.68 (-4.78; -2.39)	<0.01
No severe albuminuria	-0.88 (-1.18; -0.58)		-0.86 (-1.25; -0.48)	
Hypertension				
Hypertension	-1.41 (-1.73; -1.10)	<0.01	-1.37 (-1.70; -1.03)	<0.01
No hypertension	-0.81 (-1.14; -0.49)		-0.78 (-1.12; -0.43)	
Cardiovascular complications				
Cardiovascular complications	-1.64 (-2.17; -1.11)	0.03	-1.51 (-2.05; -0.97)	0.04
No Cardiovascular complications	-1.09 (-1.37; -0.81)		-0.97 (-1.26; -0.69)	
Retinopathy				
Retinopathy	-1.33 (-1.73; -0.93)	0.02	-1.22 (-1.65; -0.78)	0.23
No retinopathy	-0.86 (-1.22; -0.51)		-0.96 (-1.35; -0.58)	
Dyslipidemia				
Dyslipidemia	-1.18 (-1.47; -0.90)	0.13	-1.22 (-1.52; -0.92)	0.02
No dyslipidemia	-0.84 (-1.32; -0.36)		-0.69 (-1.22; -0.17)	
Diabetes therapy and clinical parameters				
Therapy				
Insulin pump	-1.33 (-1.69; -0.97)		-1.26 (-1.63; -0.89)	
ICT	-1.16 (-1.48; -0.85)	0.53	-1.06 (-1.39; -0.73)	0.44
CT	-1.23 (-1.74; -0.73)		-1.12 (-1.65; -0.59)	
Metabolic control				
HbA1c ≥ 9 % HbA1c ≥75 mmol/mol	-1.57 (-2.02; -1.12)		-1.40 (-1.88; -0.93)	
7.5 ≤ HbA1c < 9 % 58≤ HbA1c <75 mmol/mol	-1.19 (-1.54; -0.84)	<0.01	-1.21 (-1.57; -0.85)	0.04
HbA1c < 7.5% HbA1c <58 mmol/mol	-0.96 (-1.29; -0.64)		-1.02 (-1.37; -0.67)	
ACE inhibitors/ARB				
ACE inhibitors/ARB	-1.71 (-2.42; -0.99)	0.09	-1.52 (-2.24; -0.79)	0.24
No ACE inhibitors/ARB	-1.11 (-1.39; -0.82)		-1.09 (-1.38; -0.79)	
Self-monitoring				
SMBG < 4 per day	-0.92 (-1.36; -0.49)		-0.84 (-1.30; -0.39)	
4 ≤ SMBG ≤ 6 per day	-1.14 (-1.44; -0.85)	<0.01	-1.17 (-1.48; -0.87)	<0.01
SMBG > 6 per day	-1.45 (-2.11; -0.80)		-1.54 (-2.24; -0.85)	
BMI				
BMI < 30 kg/m^2	-1.08 (-1.37; -0.80)	0.04	-1.09 (-1.38; -0.79)	0.12
BMI ≥ 30 kg/m^2	-1.55 (-2.05; -1.05)		-1.47 (-2.00; -0.94)	
Physical activity				
Physical activity	-1.10 (-1.49; -0.71)	0.74	-1.21 (-1.62; -0.81)	0.62
No physical activity	-1.17 (-1.46; -0.87)		-1.12 (-1.43; -0.80)	
Smoking				

Smoking	-1.62 (-2.43; -0.83)	0.21	-1.83 (-2.65; -1.02)	0.08
No smoking	-1.29 (-1.41; -0.85)		-1.12 (-1.42; -0.83)	

Hierarchic linear regression models weighted by number of GFR measurements were fitted. Model 1 was adjusted for sex, age, duration of diabetes, migration background, and baseline GFR. Model 2 was additionally adjusted for insulin therapy, metabolic control, frequency of SMBG, BMI, diabetic comorbidities, ACE inhibitors/ARB treatment, and smoking. Results were presented as adjusted estimates (LSmeans with CI).

Figures

Figure 1

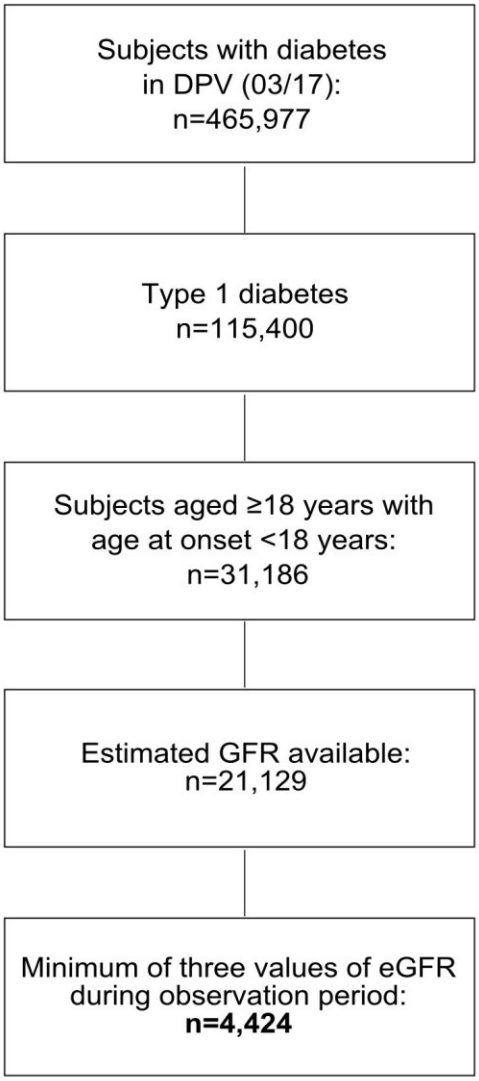
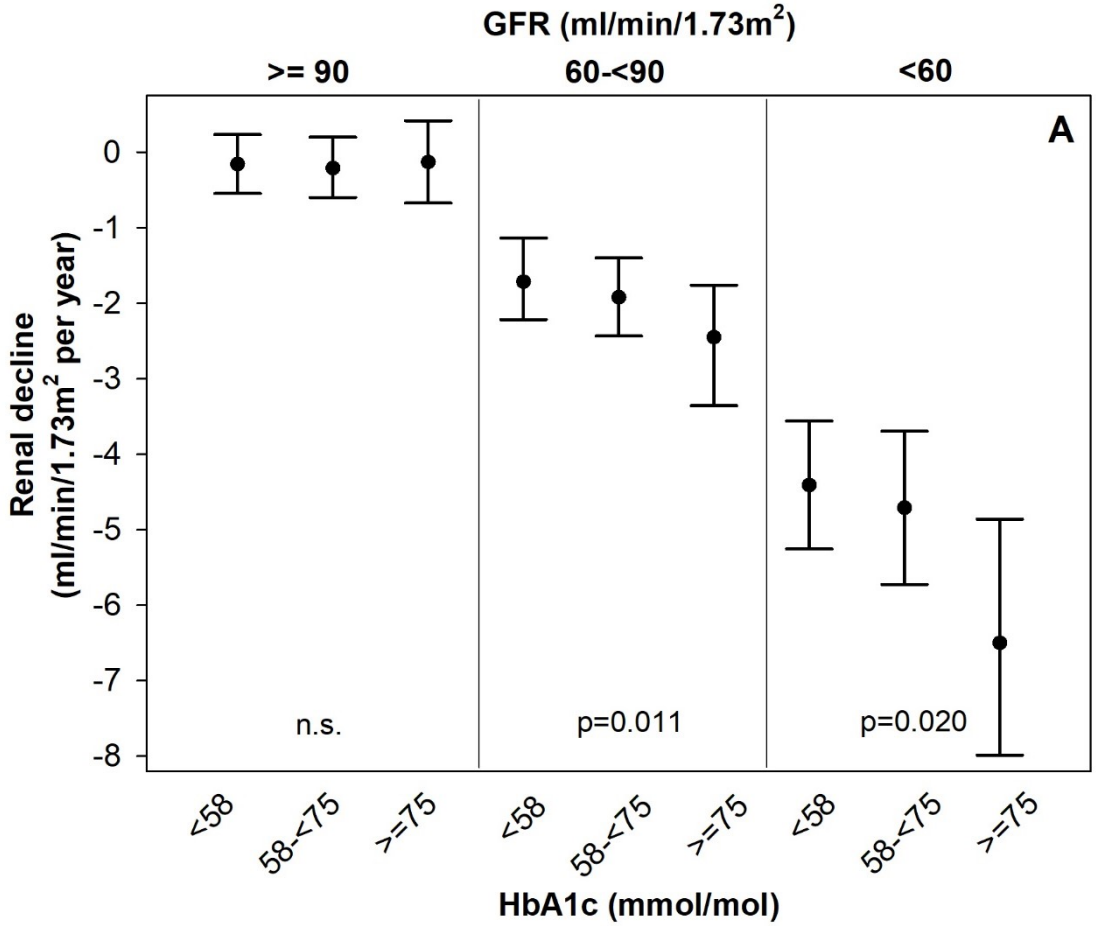


Figure 1 Patient selection of the study cohort.

Figure 2


GFR (ml/min/1.73m2)
>= 90
60-<90
<60
A
Renal decline
(ml/min/1.73m2 per year)
0
-1
-2
-3
-4
-5
-6
-7
-8
n.s.
p=0.011
p=0.020
<58
58-<75
>=75
<58
58-<75
>=75
<58
58-<75
>=75
HbA1c (mmol/mol)

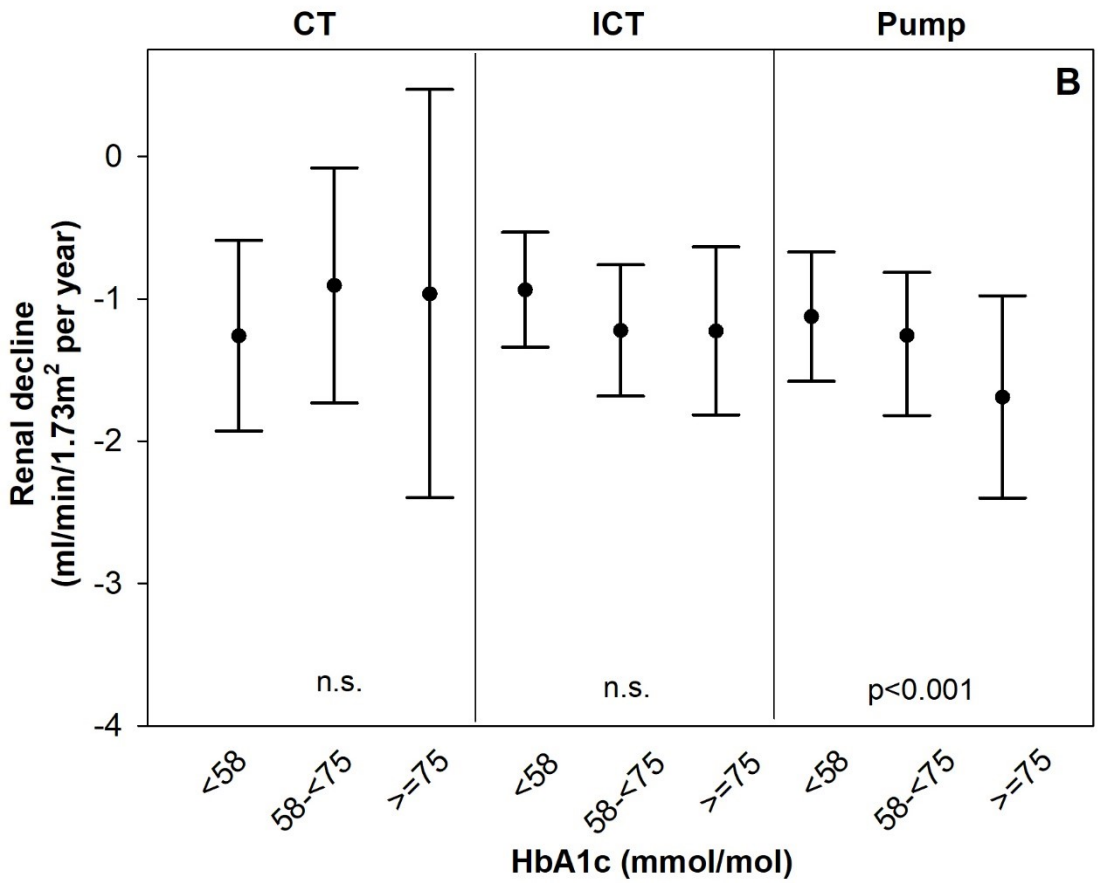


Figure 2 Kidney decline separated by HbA1c levels and strata of GFR (A) or insulin therapy (B) during follow-up. Figure shows results of hierarchic linear regression model adjusted for demographics and further covariates. Results were presented as adjusted estimates (LSmeans with CI).