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Glomerular filtration rate decline in T2DM following diagnosis. The Verona newly diagnosed diabetes study-12

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ABSTRACT

Aims: Nephropathy is a complication of type 2 diabetes, with increased albuminuria and reduced glomerular filtration rate (GFR) as biomarkers. Rates of progression to end-stage-renal disease are variable among patients. In this study we have examined the GFR decline in newly diagnosed T2DM.

Methods: A cohort of 410 patients with newly diagnosed T2DM and with at least four serum creatinine during the follow-up period were recruited. A linear model was used to calculate the decline in eGFR. A multivariable logistic model was used to identify independent predictors of rapid eGFR decline.

Results: Average follow-up was 12.4 years. The eGFR change was −0.80 ± 2.23 ml/min/1.73 m^2 per year. Patients were arbitrarily stratified into rapid decliners (≤-3.0 ml/min/1.73 m^2 per year), moderate decliners (-2.9/-1 ml/min/1.73 m^2 per year) and slow/no decliners (>-1.0 ml/min/1.73 m^2 per year). Subjects in the 3 categories were 11.4%, 27.3%, and 61.3%, respectively. Albuminuria was the stronger predictor of rapid eGFR decline.

Conclusions: A rapid decline in eGFR occurs in approximately 1 out of 10 newly diagnosed subjects. This rapid decline can be predicted by widely accessible clinical features, such as albuminuria. Identification of rapid decliners may help to reduce progression toward advanced stages of nephropathy.

1. Introduction

Diabetic nephropathy is a common complication of type 2 diabetes (T2DM) [1] and its clinical consequences, such as chronic kidney disease (CKD), nephrotic syndrome, end-stage renal disease (ESRD) and cardiovascular disease (CVD), may be severe and life threatening [2,3]. Therefore, it is important to timely identify patients with incipient nephropaty or at high risk of marked loss of renal function in order to implement strategies to stop or slow down the progression of the

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disease. Increased albuminuria and reduced glomerular filtration rate (GFR) are the classic biomarkers of nephropathy, and its progression is heralded by significant changes in these two parameters [4,5].

It is well known that albuminuria, hypertension and poor glycemic control contribute to the decline of GFR [6–8], and that nephropathy is often associated to other microvascular or macrovascular complications [9,10].

Studies exploring the decline of GFR in T2DM (6–10) have observed that patients may follow different trajectories, a small group of patients with a rapid decline of GFR and others patients who decline less rapidly. All the studies agreed on the importance of the identification of patients with a rapid decline. However, these studies have included patients with longstanding disease in whom the phenomenon is strongly influenced by prolonged exposure to hyperglycemia as well as medications used for treating diabetes and hypertension. The information of the decline of GFR in the years immediately following the diagnosis of T2DM is lacking. We believe that this information is important as the prevention of eGFR decline should be as precocious as possible.

Therefore, in the present study we evaluated changes in estimated GFR (eGFR) occurring in a cohort of T2DM patients since time of diagnosis for several years. Most importantly, we aimed to identify rapid decliners in eGFR and independent predictors of this rapid loss of renal function in order to identify patients who may benefit of a precocious implementation of preventive measures.

2. Materials and methods

2.1. *Study population*

The present study was carried out in 410 subjects enrolled in the Verona Newly Diagnosed Diabetes Study (VNDS), an ongoing study on genetics, pathophysiology and clinics of patients with newly diagnosed T2DM. Supplementary figure 1 shows the flow of study participants, while supplementary table 1 shows that the selected 410 subjects were similar, in term of the major clinical characteristics, to the all cohort. The details of study were already presented in previous publications [11,12]. In brief, patients referred to the Diabetes Clinic, embedded in the Division of Endocrinology, Diabetes and Metabolic Diseases of the University and Hospital Trust of Verona and whose disease was diagnosed in the past 6 months were offered to participate in this study. Patients of the present study had their first visit between January 1, 2002 and December 31, 2009 and continued to attend the Clinic in the following years, with at least one assessment of serum creatinine per year. The observation period of this cohort ended on December 31, 2019 and a minimum of 4 creatinine qualified subjects for inclusion in the analysis.

The clinical evidence on which the diagnosis of T2DM had been made was reviewed at the recruitment and the diagnosis was confirmed according to standard criteria. The large majority of patients were drug-naïve (about 95%). Patients older than 75 years, on insulin therapy, of non-Italian ancestry, with positive anti-glutamic acid decarboxylase antibodies and/or with history of malignancies or any severe impairment of hepatic and/or renal function were excluded from the study. All participants gave their informed consent and the study was approved by the local Ethics Committee.

3. Clinical data

Weight in kilograms divided by the square of height in meters was used to calculate the body mass index (BMI).. Blood pressure was measured with a standard mercury manometer on the right arm when sitting. Hypertension was considered when participants were taking any antihypertensive medications or their blood pressure was $\geq$ 140/90. A confirmed history of myocardial infarction, angina, coronary revascularization, stroke, transitory ischemic attack, carotid revascularization, non-traumatic amputation, gangrene and/or lower limb revascularization was considered a valid proxy for prior clinical CVD. Presence of diabetic retinopathy was investigated by indirect ophthalmoscopy after pupillary dilation by a single expert ophthalmologist.

Venous blood was drawn in the morning after an overnight fast in all patients. Serum creatinine (Jaffè rate-blanked and compensated assay), lipids, plasma glucose were assayed by standard laboratory procedures. Hemoglobin A1c (HbA1c) was measured by high performance liquid chromatography and standardized according to IFCC. Glomerular filtration rate was estimated (eGFR) using the Modification of Diet in Renal Disease equation (MDRD) [13]. An eGFR below 60 ml/min/1.73 m^2 was considered for the diagnosis of CKD. Urinary albumin excretion was measured in two early morning urine samples as the albumin-to-creatinine ratio /A/C ratio; units: mg albuminuria/g creatininuria) by an immunonephelometric method. Microalbuminuria and macroalbuminuria were defined as urinary excretion of 30–300 and > 300 mg/g, respectively. Considering the low number of subjects with macroalbuminuria, a combined variable of albuminuria that comprises the 5 subjects with macroalbuminuria plus the 47 subjects with microalbuminuria was computed for the analysis.

3.1. *Statistical analysis*

Data are presented as mean ± SD and frequency. The Anova, with the Sceffé test for multiple comparisons, and χ^2 test were used to compare baseline characteristics of participants after their stratification according to changes of eGFR across years. A linear regression analysis of time on eGFR was used to calculate the slope of the regression line for each single participants, which was then used as a proxy of the change over time. A minimum of 4 serum creatinine measurements was considered necessary for the inclusion in the analysis. Patients were stratified into three groups based upon the following values of eGFR change: rapid decliners ($\leq$-3.0 ml/min/1.73 m^2 per year), moderate decliners (-2.9/-1 ml/min/1.73 m^2), slow/no decliners (>-1.0 ml/min/1.73 m^2 per year). The thresholds were chosen on the basis of previous studies that reported that an eGFR loss of ($\leq$-3.0 ml/min/1.73 m^2 per year reflects three times more rapid decline than expected by normal aging (about −1.0 ml/min/1.73 m^2 per year) [8].

To identify predictors of the rapid decline of eGFR, a multivariable logistic regression analysis was performed with the status of rapid decliner as dependent variable and covariates statistically different in the 3 categories of eGFR change or biologically plausible as independent variables.

Statistical analysis was performed with SPSS statistical package software. P values < 0.05 were considered statistically significant.

4. Results

The main clinical features of the cohort are presented in Table 1. Men were more represented than women, mean age was approximately 60 yrs, as many as 50% of subjects were obese and HbA1c was mildly elevated in most subjects. At baseline 37 patients (9%) had eGFR < 60 ml/min/1.73 m^2. 47 patients (11.9%) had microalbuminuria, 5 had macroalbuminuria (1.3%), 52 (13.2%) micro or macroalbuminuria, 16 (4.0%) had retinopathy (non-proliferative in all of them), 41 (10%) had a history of clinical cardiovascular disease (myocardial infarction, stroke, etc). As many as 70% of patients had hypertension and 58% were treated for high blood pressure. The percentages of hypertensive treatment were 68.1% in the rapid decline, 60.0% in moderate decline and 56.4% in slow/no decline (p = 0.312). Fifteen percent of patients were assuming statins.

The median follow-up period was 12.4 years (range 2.4–16.8). During this period the minimum number of creatinine measurements was 4 and the maximum 17, with an average of 10.

Table 1 illustrates main clinical characteristics of patients after stratification according to eGFR change. As compared to slow/no decliners patients with a rapid decline were significantly older, more frequently of male gender, had higher systolic blood pressure, and baseline eGFR. They also had more frequently hypertension, micro/macroalbuminuria, retinopathy and CVD. Moderate decliners had HbA1c higher than slow/no decliners but no other significant difference when compared to this group. The percentage of subjects with either baseline eGFR lower than 60 ml/min/1.73 m^2 (37 subjects) or higher than 120 ml/min/1.73 m^2 (24 subjects) were not significantly different among the three groups.

The multivariate logistic analysis (Table 2) showed that retinopathy, micro/macroalbuminuria, systolic blood pressure and baseline eGFR at baseline were significant predictors of a rapid decline in eGFR. The results of the multivariate analysis did not change when in the model were included antihypertensive and statin therapy. Moreover, the inclusion of a categoric variable of subjects with hyperfiltration at baseline (eGFR > 120 ml/min/1.73 m^2) compared to those with eGFR $\leq$ 120 ml/min/1.73 m^2 instead of eGRF, showed a tendency of an increased risk of rapid decline in subjects with glomerular hyperfiltration (OR 2.0, CI 95% 0.6–7.3; p = 0.285), even though a clear tendency to a higher prevalence of subjects with glomerular hyperfiltration was observed in the rapid decline group.

5. Discussion

At the best of our knowledge, the present is the first study examining the changes of eGFR in the years immediately following diagnosis of T2DM and establishing different categories of patients according to kidney function loss. The UKPDS, the largest study in newly diagnosed type 2 diabetes,

Table 1 – Clinical characteristics of the 410 newly diagnosed type diabetes according to the eGFR trend in the year immediately following the diagnosis.

	All subjects	Slow/No decline n = 251	Moderate decline n = 112	Rapid decline n = 47	p
Age (years)	58.6 ± 8.9	57.8 ± 9.1[a]	59.1 ± 8.7	61.5 ± 7.8[a]	0.028
Sex (F,%)	32.4	29.1	35.7	42.6	0.133
BMI (Kg/m^2)	30.2 ± 5.1	30.1 ± 5.0	30.2 ± 5.0	30.8 ± 5.5	0.717
SBP (mmHg)	137.6 ± 18.1	135.4 ± 16.4[a]	139.1 ± 18.5	145.6 ± 22.9[a]	0.001
DBP (mmHg)	84.4 ± 9.2	84.1 ± 9.0	84.5 ± 9.4	85.7 ± 10.3	0.538
HbA1c (mmol/molHb)	52.2 ± 13.5	50.7 ± 12.1[b]	55.0 ± 15.8[b]	53.8 ± 14.1	0.017
Cholesterol (mmo/l)	5.0 ± 1.0	4.9 ± 1.0	5.0 ± 0.9	4.9 ± 1.0	0.661
LDL-Cholesterol (mmol/l)	3.1 ± 0.9	3.0 ± 0.8	3.2 ± 0.9	3.0 ± 1.0	0.228
HDL-Cholesterol (mmol/l)	1.20 ± 0.35	1.18 ± 0.34	1.20 ± 0.30	1.26 ± 0.52	0.300
Triglycerides (mmol/l)	1.6 ± 1.0	1.7 ± 1.1	1.6 ± 0.8	1.6 ± 0.8	0.464
Baseline $eGFR_{MDRD}$ (ml/min 1.73 m^2)	84.0 ± 21.2	83.4 ± 19.7[a]	82.5 ± 19.6	91.0 ± 30.0[a]	0.052
eGFR change (ml/min 1.73 m^2/year)	−0.80 ± 2.24	0.49 ± 1.09	−1.83 ± 0.59	−5.23 ± 2.36	NA
$eGFR_{MDRD} \leq$ 60 ml/min/1.73 m^2 (%)	9.0	7.6	12.5	8.5	0.315
$eGFR_{MDRD}$ > 120 ml/min 1.73 m^2) (%)	5.9	4.8	7.1	8.5	0.481
Hypertension (%)	70.2	68.6	70.9	83.0	0.131
Albuminuria (%) (n = 395)	13.2	11.2	13.9	30.2	0.004
Retinopathy (%) (n = 397)	4.0	3.7	1.8	11.4	0.023
Prior clinical cardiovascular dis. (%)	41	10.0	7.2	17.0	0.171

BMI: body mass index; SBP:systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; LDL: low density lipoprotein; HDL: high density lipoprotein; eGFR: estimated glomerular filtration rate; Albuminuria: combined variable of micro and macroproteinuria.a and b at the apex refers to the p < 0.05 for multiple comparisons (test Sceffé).

Table 2 – Multivariate logistic regression analysis with rapid decline of eGFR as dependent variable.

	OR (IC 95%)	p
Age (per year)	1.03 (0.99–1.08)	0.181
Sex (female/male)	1.94 (0.91–4.11)	0.084
BMI (per Kg/m^2)	1.01 (0.93–1.09)	0.900
PAS (per mmHg)	1.03 (1.00–1.06)	0.034
PAD (per mmHg)	0.98 (0.93–1.03)	0.371
Hba1c (per absolute 1%)	0.99 (0.73–1.34)	0.938
eGFR (per ml/min 1.73 m^2)	1.02 (1.00–1.03)	0.017
Micro-macroalbuminuria (yes/no)	3.10 (1.29–7.48)	0.012
Retinophaty (yes/no)	3.97 (1.10–14.41)	0.036
Prior clinical cardiovascular disease (yes/no)	2.49 (0.89 – 6.97)	0.084

eGFR, estimatec glomerular filtration rate; BMI, body mass index, PAS, systolic blood pressure; PAD, diastolic blood pressure; HbA1c, glycosylated hemoglobin.

focused on incidence and progression of micro/macroalbuminuria, renal failure (defined as a plasma creatinine > 250 μmol/l not related to an acute clinical event), dialysis and death from renal diseases, but did not examine the rates of decline in eGFR [14,15].

We found that approximately 1 out of 10 newly diagnosed patients with T2DM had a rapid decline in eGFR (≤-3 ml/min/1.73 m^2) in the years following time of diagnosis. This proportion was not much different (11 vs. 15%) from that we found in patients with T2DM of longer duration and preserved kidney function at baseline [8]. The proportion, however, is definitely lower than the 50–60% observed in patients with CKD (9,10). In our study moderate decliners (-1.0 / −2.9 ml/min/1.73 m^2) amounted to 27%, which means that as many as 1 patients out of 4 is predicted to have an substantial reduction in eGFR over 20 years (ranging ~ 20 to ~ 60 ml/min/1.73 m^2), assuming a linear loss of function across time. Overall, up to 40% of patients with newly diagnosed T2DM is expected to develop a substantial or severe impairment of kidney function in the 20 years following diagnosis, with a fraction of them most probably reaching ESRD.

It is not surprising that in newly diagnosed T2DM a sizable subgroup of patients is already at risk of a more or less rapid decline in GFR because the biological onset of the disease is estimated to antedate the clinical diagnosis by several years [16]. Accordingly, many patients with T2DM already have retinopathy, nephropathy, somatic and/or autonomic neuropathy and/or clinical or preclinical CVD at time of diagnosis [12]. Moreover, T2DM is often associated to features of the Metabolic Syndrome, such as hypertension, atherogenic dyslipidemia, microalbuminuria, insulin resistance, abdominal obesity [17], all conditions which were related to an increased risk of CKD, as also shown in a large observational cohort of type 2 diabetes representative of real life clinical practice in Italy [18–20].

Not surprisingly, and in accordance with previous reports [7,8], in our study micro/macroalbuminuria was the most important risk factor for rapid decline of eGFR. Albuminuria, indeed, is not only a statistical marker but also a causative factor precipitating CKD [21]. This points out the need to periodically measure albuminuria and implement strategies to reduce it with effective anti-hypertensive and anti-hyperglycemic medications [22–25].

Hypertension conveyed an increased risk for a more rapid decline in eGFR. The result confirms previous findings [26] and stress the concept that diabetes care includes a careful control of blood pressure and not only HbA1c in order to protect the kidney.

In our study the presence of retinopathy was among risk factors for a rapid decline in eGFR. Retinopathy may be considered a marker of a diffuse microvascular disease [27,28]. Therefore, it is important to give a value to the finding of retinopathy at time of diagnosis of T2DM. It is indeed a valuable clinical marker of patients who require a well scheduled staging also of kidney function and deserve a more powerful control of all modifiable risk factors.

The results of our study are clinically relevant because they point out the need of a comprehensive assessment of kidney function when T2DM is first diagnosed and a strict surveillance of patients who have risk factors for its rapid decline (e.g., micro/macroalbuminuria, hypertension, poor glucose control, retinopathy), without any optimism when finding a high/normal eGFR because it also conveys an increased risk of more rapid decline in kidney function. As shown by previous studies, glomerular hyperfiltration remarkably contributes to kidney disease in T2DM [29,30].

The present study has major limitations: lack of data on ACE inhibitors or ARRB and the new drugs SGLT-2 inhibitors or GLP-1 agonists during the follow-up period, drugs that may modify the eGFR decline. GFR was estimated and not directly measured but this limitation is common to the vast majority of studies involving hundred or thousand patients. On the other hand, subjects belonging to the age category in which the estimate of GFR is less solid (e.g., >75 years) were not included in this study. Moreover, it should be acknowledged that eGFR measurements may vary significantly from time to time within the same subjects even for transient conditions (for instance, dehydration, drugs). The slope of eGFR for each single patient was derived from a linear regression model. Subjects were selected if they had more than four eGFR determinations during the study period, this selection limits the generalizability of the results.

Strengths of the study are the prospective design with serial assessment of serum creatinine for several years, the quite large number of subjects examined, the focus on newly diagnosed drug-naïve T2DM the comprehensive assessment

of several clinical features with standardized methods, the measurement of serum creatinine and all biochemical parameters in the same laboratory.

In conclusion, our study demonstrates that, a rapid decline of renal function can occur in a sizable proportion of subjects with T2DM in the years immediately following the diagnosis. This decline can be predicted using a simple clinical approach based upon the assessment of albuminuria, eGFR, blood pressure and retinal status. Finding micro-macroalbuminuria, hypertension, glomerular hyperfiltration and retinopathy should prompt caregivers to implement effective strategies aiming at protecting the kidney of people with newly diagnosed T2DM.

Disclosures

All authors have nothing to disclose.

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Author's contributions

GZ,MT: were responsible for the research idea, study design, data analysis and writing the manuscript.IP,CB,VC,CN,FP,IP,VS,DT,ER,GDP,CB: were responsible for generating data and the preparation of the database. RCB, EB: were responsible for supervision, for critically reviewing the manuscript and mentorship.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.108778.

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