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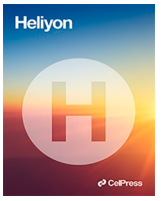

Research article

Chronic kidney disease progression in diabetic patients: Real world data in general practice

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ABSTRACT

Aims: the aim of the study was to analyze glomerular filtration ratio (GFR) changes in diabetic patients assisted by General Practitioners (GPs) evaluating the risk factors related to glomerular function.
Methods: patients with diabetes with at least three recorded values of creatinine were recruited in the study and GFR values were estimated. The quarterly percentage change in GFR for each patient was estimated. Nephrotoxic drugs were identified, and glucose-lowering drugs use was described. Linear regression analyses were performed to identify eGFR changes predictors.
Results: a total of 545 patients with diabetes were selected. According to the last eGFR values 64 (11.7 %) patients were classified in G1 stage, 277 (50,8 %) in G2, 175 (32.1 %) in G3a, 25 (4.6 %) in G3b and only 4 (0.7 %) in G4. Patients treated with at least one glucose-lowering drugs were 479 (87.9 %), most of them with biguanides (67.0 %). At least one nephrotoxic drug prescription was recorded in 524 (96.1 %) patients; proton pump inhibitors (74.7 %) and NSAIDs (71.6 %) were the most prescription classes. Heart failure, diabetes duration and preserved GFR values were related to reduced eGFR values.
Conclusions: patients with diabetes should be more carefully observed regardless of kidney risk factors and GFR values in clinical practice.

1. Introduction

The global prevalence of diabetes mellitus (DM) has increased over the past few decades and is now estimated to exceed 10 % worldwide. The International Diabetes Federation estimated that 537 million of people were affected by diabetes in 2021, with an expected increase of 784 million by the year 2045 [1]. Diabetes is commonly related to Chronic Kidney Disease (CKD) and their association reduces the quality of life of the affected patients as well as their life expectancy and survival. In fact, the prevalence of CKD

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among patients with diabetes is >25 % and the respective 40 % might develop CKD during their lifetime; previous studies already showed that the prevalence of CKD related to diabetes proportionally increased with respect to the increased prevalence of diabetes [2,3], which represents the most common cause of kidney failure up to kidney transplantation and/or dialysis [4]. CKD not only increases the risk of kidney failure but also is a risk factor for the development of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) and all-cause mortality among people with diabetes [5].

In order to manage CKD progression in diabetic patients, the ADA guidelines recommend the screening for renal function and albuminuria, every year starting on the day of diagnosis of diabetes [6], using the CKD-Epidemiology Collaboration (CKD-EPI) formula to estimate the glomerular filtration rate (eGFR) [7]. The recent ADA guidelines recommend to achieve the target glycated hemoglobin (HbA1c) between 6.5 % and 8.0 % in patients with diabetes; however, the goal should be personalized according to the individual characteristics of patients, such as CKD stage and the presence of other risk factors [8]. Moreover, several clinical studies showed that HbA1c levels <7 % were associated with a reduced risk of CKD progression [8,9]. In addition to glycemic management [8], to avoid nephrotoxic drugs use could be considered an additional preventive intervention to reduce CKD progression risk. Indeed, drug-induced nephrotoxicity is one of the major pathogenic factors for CKD, acute renal failure, and end-stage renal disease, especially in patients with risk factor such as diabetes [10]. In the light of these evidences, the management of patients with diabetes needs to start in primary care, with a specific focus on the prevention and screening of all risk factors as-sociated with diabetes including the renal failure [11]. Therefore, the aim of the present study was to analyze eGFR changes in a cohort of patients with diabetes followed by General Practitioners (GPs) through the evaluation of the risk factors related to glomerular function.

2. Materials and methods

2.1. Study population

A retrospective observational study was carried out using the clinical reports of patients registered in the lists of 18 GPs belonging to the Audit & Research Messina Primary Care Group from 2018 to 2022. The study protocol was approved by the local Ethical Committee of Messina University Hospital (n° prot. N.5020; date of approval June 29th, 2020). All patients affected by diabetes, identified using the recorded International Classification of Diseases 9th revision (ICD-9) code = 250.xx, with at least three recorded values of creatinine were recruited in this study. The following demographic and clinical data were collected.

- encrypted patient code, age, gender, and body mass index (BMI);
- information on lifestyle (smoking and alcohol consumption);
- laboratory exams: serum creatinine, fasting plasma glucose (FPG), HbA1c, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides;
- registered diagnosis of comorbidities codified using the ICD-9;
- all drug prescriptions, classified according to the Anatomical Therapeutic and Chemical (ATC) Classification System.

GFR values were estimated using CKD-epidemiology collaboration (CKD-EPI) formula (eGFR). In accordance with the recent guidelines, HbA1c <7 % and LDL-C <70 mg/dL have been defined as the target values [8]. The cohort of patients was classified according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines based on the last eGFR values. In particular, patients were classified into stages G1 (eGFR ≥90 ml/min/1.73 m^2), stage G2 (eGFR 60–89 ml/min/1.73 m^2), stage G3a (eGFR 45–59

Table 1
The types of kidney injury, together with the ascribed drugs that trigger them.

	Drugs	
Tubular epithelial injury via intracellular accumulation	amphotericin B, non-lysosomal gentamicin kanamycin streptomycin tobramycin vancomycin	cisplatin carboplatin nedaplatin tenofovir cidofovir adenofovir
Tubular obstruction by crystals and casts containing drugs and their metabolites	sulfadiazine methotrexate triamterene vancomycin	Indinavir atazanavir ciprofloxacin
Interstitial nephritis	Antibiotics • Penicillins • Cephalosporins • Quinolones • Vancomycin • Rifampicin	NSAIDs Proton pump inhibitors Immune checkpoint inhibitors Thiazide diuretics Lithium Anti-epileptic drugs • Phenytoin • valproic acid • carbamazepine Allopurinol

ml/min/1.73 m^2), G3b (eGFR 30–44 ml/min/1.73 m^2), G4 (eGFR 15–29 ml/min/1.73 m^2), and G5 (eGFR <15 ml/min/1.73 m^2). The quarterly percentage change in eGFR (eGFR % change) for each patient during the study period was estimated.

2.2. Nephrotoxicity drugs selection

Drug-induced nephrotoxicity develops according to three different mechanisms: (a) Tubular epithelial injury via intracellular accumulation, (dose-dependent mechanism); (b) tubular obstruction by crystals or casts containing drugs and their metabolites (dose-dependent mechanism); (c) interstitial nephritis induced by drugs and their metabolites (dose-independent mechanism). Nephrotoxic drugs were identified according to literature reviews using the Medical Subject Headings (MeSH) terms "nephrotoxic drug" and "drug-induced renal failure" as well as suggested by Kwiatkowska et al. [12].

The types of kidney injury, together with the ascribed drugs that trigger them, are reported in Table 1.

From Kwiatkowska et al. [12].

2.3. Statistical analyses

A descriptive analysis was performed to compare all characteristics of the study population (e.g., age, gender, comorbidity, drug prescriptions) between patients with a reduction (negative eGFR % change) and an increase (positive eGFR % change) of kidney function. Due to a not normal distribution of some numerical variables, verified using the Kolmogorov–Smirnov test for normality, a non-parametric approach was always adopted. Absolute and relative frequencies were evaluated for the categorical variables, while medians with the first (Q1) and third (Q3) quartile were calculated for continuous numerical variables. The Mann–Whitney *U* test for independent sample and two-tailed Pearson chi-squared test were carried out to compare continuous numerical variables and categorical variables, respectively. Univariate logistic regression models were performed to evaluate the probability of eGFR reduction according to GFR stage. Odds ratios (ORs) with 95 % CIs were calculated for each co-variate of interest in the univariate (crude OR) model. Multivariate linear regression analyses were performed to identify variables that influenced the eGFR % changes. Statistical significance was considered when p-value was <0.05. All analyses were performed by using SPSS version 23.0 statistical package (IBM Corp., SPSS Statistics, Armonk, NY, United States).

3. Results

3.1. Characteristics of patients and laboratory measures

A total of 2679 patients with diabetes were identified and 545 (20.3 %) had at least 3 registered serum creatinine value in the five years of the study. The selected patients were aged 74 years (67–80) and 50.5 % were females. The median (Q1-Q3) diabetes duration

Table 2
Demographic and clinical characteristics of patients with diabetes stratified by kidney function.

	Increased kidney function N = 225	Reduction kidney function N = 320	P Value	Total N = 545
Age (years)	75 (67–81)	74 (67–81)	0.586	74 (67–80)
Gender (F), n (%)	106 (47.1)	169 (52.8)	0.190	275 (50.5)
SBP (mmHg)	140 (130–150)	137 (125–145)	0.150	140 (130–150)
DBP (mmHg)	80 (70–85)	80 (70–85)	0.852	80 (70–85)
BMI (Kg/m^3)	27.5 (25.1–32.0)	28.9 (26.4–32.4)	0.011	28.4 (26.1–32.3)
Glycemia (mg/dL)	120.0 (102.0–148.0)	124.5 (104.0–152.0)	0.180	121.0 (103.0–150.0)
HbA1c (%)	6.8 (6.2–7.5)	6.7 (6.1–7.4)	0.342	6.7 (6.1–7.5)
Cholesterol total (mg/dL)	158.0 (138.0–186.0)	157.0 (136.0–186.0)	0.998	157.0 (137.0–186.0)
HDL-C (mg/dL)	46.0 (40.0–53.0)	46.0 (39.0–56.0)	0.437	46.0 (39.0–55.0)
Triglycerides (mg/dL)	121.0 (88.0–160.0)	113.0 (83.0–161.3)	0.386	115.0 (86.0–160.15)
LDL-C (mg/dL)	88.0 (63.0–111.0)	85.0 (66.0–105.0)	0.973	86.0 (64.0–107.0)
Comorbidities				
Neoplasm	39 (17.3)	55 (17.2)	0.965	94 (17.2)
Dyslipidemia	136 (60.4)	197 (61.6)	0.792	333 (61.1)
Mood disorders	95 (42.2)	139 (43.4)	0.778	234 (42.9)
Hypertension	186 (82.7)	170 (74.4)	0.595	456 (83.7)
Ischemic heart disease	53 (23.6)	83 (25.9)	0.527	136 (25.0)
Heart failure	8 (3.6)	28 (8.8)	0.016	36 (6.6)
Cerebrovascular disease	82 (36.4)	129 (40.3)	0.361	211 (38.7)
Atherosclerosis	39 (17.3)	57 (17.8)	0.885	96 (17.6)
Chronic respiratory diseases	74 (32.9)	101 (31.6)	0.744	175 (32.1)
Arthritis and arthrosis	79 (35.1)	136 (42.5)	0.082	215 (39.4)
Osteoporosis	72 (32.0)	111 (34.7)	0.513	183 (33.6)
Obesity	34 (15.1)	62 (19.4)	0.198	96 (17.6)

BMI= Body mass index, DBP = Diastolic blood pressure, HbA1c = Glycated Hemoglobin, HDL-C = High Density Lipoprotein Cholesterol, LDL-C = Low Density Lipoprotein Cholesterol, SBP= Systolic blood pressure.

was 9 (5–14) years, and 100 patients (18.3 %) had a CKD diagnosis (Table 2).

According to the last eGFR values 64 (11.7 %) patients were classified in G1 stage, 277 (50,8 %) in G2, 175 (32.1 %) in G3a, 25 (4.6 %) in G3b and only 4 (0.7 %) patients were in G4 stage. A lower probability to develop eGFR reduction was observed in patients in G2 (OR [95 % CI]: 0.56 [0.33–0.94]) and G3a (OR [95 % CI]: 0.35 [0.20–0.61]) stages than in G1 stage patients (Table 3).

Range codified by each eGFR category: G1 ≥90 ml/min/1.73 m^2; G2 between 60 and 89 ml/min/1.73 m^2; G3a between 45 and 59 ml/min/1.73 m^2; G3b between 30 and 44 ml/min/1.73 m^2; and G4 between 15 and 29 ml/min/1.73 m^2.

The median (Q1-Q3) clinical and laboratory parameters were as follows: FPG, 121.0 (103.0–150.0) mg/dl; HbA1c, 6.7 (6.1–7.5) %; LDL, 86.0 (64.0–107.0) mg/dl; HDL, 46.0 (39.0–55.0) mg/dl; triglycerides, 115.0 (86.0–160.5) mg/dl; and total cholesterol, 157.0 (137.0–186.0) mg/dl; the SBP/DBP was 140/80 (130/70–150/85) mmHg, and BMI 28.4 (26.1–32.3) Kg/m^2. In addition, 205 (37.6 %) patients did not reach the HbA1c target (<7 %) and 372 (68.3 %) did not achieve the LDL-C target. The main comorbidity was hypertension (N = 456, 83.7 %), followed by dyslipidemia (N = 333, 61.1 %) and mood disorders (N = 234, 42.9 %).

The median eGFR % change was −0.29 (−1.40/0.79) % and a reduction of eGFR was observed in 320 (58.7 %) patients. Patients with eGFR reduction had higher BMI values (median [Q1-Q3]:28.9 [26.4–32.4] vs 27.5 [25.1–32.0]; p = 0.011) and were more affected by HF (3.6 % vs 8.8 %; p = 0.016) (Table 2).

3.2. Glucose lowering drugs use

Patients treated with at least one glucose lowering drugs were 479 (87.9 %); in particular, 88 (18.4 %) were treated with both insulin (ATC III level = A10A*) and oral hypoglycemic agents (ATC III level = A10B*), 30 (6.3 %) with insulin alone and 361 (75.3 %) with oral hypoglycemic agents alone.

The most widely used classes of oral hypoglycemic drugs were biguanides (ATC IV level = A10BA*) (N = 365; 67.0 %) followed by sulfonylureas (ATC IV level = A10BB*) (N = 100; 18.3 %) and other hypoglycemic drugs (ATC IV level = A10BX*) (N = 98; 18.0 %). No significant differences in glucose lowering drugs users were observed between patients with a reduction of GFR compared to patients with increased renal function. (Table 4).

3.3. Nephrotoxic drugs use

During the study period, 524 (96.1 %) patients received at least one nephrotoxic drug prescription. The most used classes of nephrotoxic drugs were proton pump inhibitors (PPIs, ATC = A02BC*) (N = 407; 74.7 %) followed by nonsteroidal anti-inflammatory drugs (NSAIDs, ATC = M01*) (N = 390; 71.6 %) and antimicrobials (ATC = J01*) (N = 388; 71.2 %). In particular, Pantoprazole (N = 172; 31.6 %) was the most widely used PPI, while the mainly used NSAIDs were acetic acid derivatives and related substances (N = 245; 45.0 %) and propionic acid derivatives (N = 232; 42.6 %); quinolones (N = 275; 50.5 %) and cephalosporins (N = 221; 40.6 %) were the most used antibiotics. Allopurinol was prescribed in 196 (36.0 %) patients (Table 5).

3.4. Relationship between risk factors and eGFR changes

The concurrence of HF was an independent predictor of reduced eGFR % values (B = −1.779; p = 0.001). Moreover, diabetes duration and a higher GFR value recorded at start of study were directly related with the reduction of eGFR % values (B = −0.046; p = 0.029 and B = −0.032; p < 0.001, respectively) (Table 6).

4. Discussion

The present study provides an overview of diabetes treatment in clinical practice over the past 5 years, highlighting the rate of decline in renal function. Diabetes is associated with an increased risk of impaired glomerular filtration and progressive CKD [13]. The normal rate of decline in eGFR is doubled in patients with diabetes with chronic renal failure and may exceed 3 mL/min/1.73 m^2 [14]. In our study, kidney function decline (indicated as percentage of decline) was extremely variable and is greater in subjects with a pre-served kidney function. In fact, a decline in renal function was observed in 320 (58.7 %) patients with a median eGFR reduction of −0.29 % every three months with respect to the values observed at baseline. In particular, a significant lower probability of eGFR reduction was observed in patients in advanced stages of CKD than patients in G1 stage. Furthermore, the results of the multivariate linear regression analysis highlight a correlation between a good state of glomerular filtration and the possible risk of percentage

Table 3
Patients with diabetes stratified by GFR stage and probability of decline eGFR value.

GFR stage, n (%)	First evaluation of eGFR value	Last evaluation of eGFR value	OR (95 % CI) Decline eGFR value
G1	89 (16.3)	64 (11.7)	ref
G2	286 (52.5)	277 (50.8)	0.56 (0.33–0.94)
G3a	157 (28.8)	175 (32.1)	0.35 (0.20–0.61)
G3b	13 (2.4)	25 (4.6)	0.43 (0.13–1.41)
G4	/	4 (0.7)	/

Table 4
Classes of glucose lowering drugs (ATC level IV) used by patients with diabetes stratified by kidney function.

Value: n (%)	Increased kidney function N = 225	Reduction kidney function N = 320	P Value	Total N = 545
Glucose lowering drugs users	193 (85,8)	286 (89,4)	0,205	479 (87.9)
Insulin				
Insulin and analogues; fast acting	32 (14,2)	58 (18,1)	0,227	90 (16,5)
Insulin and analogues; intermediate or long action	4 (1,8)	9 (2,8)	0,436	13 (2,4)
Insulin and analogues; slow acting	43 (19,1)	66 (20,6)	0,664	109 (20,0)
Oral glucose lowering drugs				
Alpha glucosidase inhibitors	21 (9,3)	33 (10,3)	0,706	54 (9,9)
Biguanides	142 (63,1)	223 (69,7)	0,108	365 (67,0)
DPP-4 inhibitors	20 (8,9)	27 (8,4)	0,853	47 (8,6)
GLP-1 analogues	23 (10,2)	30 (9,4)	0,742	53 (9,7)
Oral hypoglycemic associations	26 (11,6)	41 (12,8)	0,660	67 (12,3)
Other hypoglycemic agents	45 (20,0)	53 (16,6)	0,304	98 (18,0)
SGLT-2 inhibitors	13 (5,8)	22 (6,9)	0,607	35 (6,4)
Sulfonylureas	39 (17,3)	61 (19,1)	0,608	100 (18,3)
Thiazolidiones	12 (5,3)	12 (3,8)	0,375	24 (4,4)

DPP-4 = Dipeptidyl peptidase 4, GLP-1 = Glucagon-like peptide-1, SGLT-2 = Sodium-glucose co-transporter-2, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, CI = confidence interval, OR= Odds Ratio.

Table 5
Users of Nephrotoxic drugs.

Drugs	Patients, 545 (%)
Antibiotics	388 (71.2)
Penicillins	116 (21.3)
Cephalosporins	221 (40.6)
Quinolones	275 (50.5)
Vancomycin	1 (0.2)
Rifampicin	5 (0.9)
NSAIDs	390 (71.6)
Acetic acid derivatives	245 (45.0)
Oxicam derivatives	63 (11.6)
Propionic acid derivatives	232 (42.6)
COXIB	148 (27.2)
Others NSAIDs	68 (12.5)
Methotrexate	10 (1.8)
Proton pump inhibitors	407 (74.7)
Omeprazole	153 (28.1)
Pantoprazole	172 (31.6)
Lansoprazole	116 (21.3)
Rabeprazole	19 (3.5)
Esomeprazole	100 (12.3)
Thiazide diuretics	17 (3.1)
Lithium	2 (0.4)
Anti-epileptic drugs	20 (3.7)
Valproic acid	17 (3.1)
Carbamazepine	3 (0.6)
Allopurinol	196 (36.0)

NSAIDs = Non-steroidal anti-inflammatory drugs.

reduction in GFR values. This result is in accordance with an Italian observational study that showed the greatest renal function decline in 35.6 % patients in G1 stage and in 13.8 % subjects in G4 stage [15]. However, eGFR levels were found to progressively decrease starting from the G3a stage, especially in patients with micro- or macroalbuminuria compared to normoalbiminuria [14]. Renal function may be affected by initiation factors (hyperglycemia and acute renal failure, also induced by drugs) and factors of progression (hypertension, HF, dietary factors and obesity) as well as by susceptibility factors (age, sex, race/ethnicity and family history) that contribute to its decline [13]. Hyperglycemia and hypertension represent the main risk factors associated with CKD progression, however in our study both HbA1c and hypertension were not significantly correlated with eGFR changes. This opposing result could be attributed to GPs careful attitude in monitoring both the glycemic (HbA1c: 6.7 % [6.1%–7.5 %]) and the blood pressure (SBP/DBP: 140/80 mmHg [130/70 mmHg −150/85 mmHg]) profile. However, regardless of the glycemic and blood pressure control of the patients in the study, a direct correlation was found between the duration of diabetes and the percentage decline of the kidney function. Different studies [16–18] have shown that people with younger age at diabetes diagnosis are an increased risk of micro-vascular complications during lifetime than people with an older age at diagnosis. In particular, a recent meta-analysis demonstrated a 6 % of decrease the nephropathy risk for each 1-year increase in age at diabetes diagnosis [17].

Table 6
Correlations between risk factors and eGFR % changes.

	B	P Value
Age (years)	−0,024	0.128
Sex (F), n (%)	−0,301	0.254
BMI (Kg/m3)	−0,044	0.076
HbA1c (%)	0,107	0.400
Hypertension	0,331	0.404
Heart failure	−1779	0.001
Diabetes duration	−0,046	0.029
First GFR value	−0,032	<0.001
Glucose lowering class		
Insulin and analogues; intermediate or long action	−0,027	0.618
Insulin and analogues; fast acting	−0,023	0.338
Insulin and analogues; long acting	0,021	0.211
Biguanides	−0,005	0.469
SGLT-2 inhibitors	−0,041	0.196
GLP-1 analogues	−0,016	0.341
Alpha glucosidase inhibitors	−0,008	0.546
Sulfonylures	−0,010	0.542
DPP-4 inhibitors	−0,013	0.560
Thiazolidiones	−0,010	0.764
Other hypoglycemic agents	0,023	0.119
Oral hypoglycemic associations	0,020	0.156
Nephrotoxic drugs		
Diuretics	−0,094	0.197
Antiepileptic	0,003	0.675
Anti-inflammatory and anti-rheumatic	0,002	0.474
Allopurinol	−0,016	0.309
Antimybacterial	0,351	0.680
PPIs	0,003	0.635
Antibacterial for systemic use	−0,015	0.682

BMI= Body mass index, HbA1c = Glycated Hemoglobin, SGLT-2 = Sodium-glucose cotransporter-2, GLP-1 = Glucagon-like peptide-1, DPP-4 = Dipeptidyl peptidase 4, PPIs = Proton pump inhibitors.

A further and already known risk factor related to the decline in renal function is a clinical condition of HF. Indeed, different studies showed that CKD and HF, separately and in combination, are associated with severe symptoms worsening and high cardiovascular risk, mortality risk and healthcare costs, particularly in patients with diabetes [19–21]. Moreover, the serious-ness of these diseases is further accentuated because a failing heart could lead to kidney failure, and vice versa, through inter-organ crosstalk [22], driving a vicious cycle resulting in cardio-renal syndrome [23]. In our study, we found that HF is an independent factor of renal function decline in patients with diabetes, therefore, the optimization of the classic therapeutic strategies used for DM might improve the clinical condition of patients affected by both HF and CKD. In this context, Sodium glucose cotransporter-2 (SGLT-2) inhibitors belong to a new class of glucose-lowering drugs, which have shown consistent risk-beneficial effects on hospitalization and on the management patients with HF [24–26] and CKD [27–30], thus preventing their worsening. In fact, SGLT-2 inhibitors are one of the main classes of drugs recommended by the ADA guidelines as the first-line treatment for glycemic control in patients with CVD and CKD, in replacement of metformin which remains the main oral hypoglycemic agent recommended to patients with diabetes [31]. However, several studies have shown poor under-prescription of SGLT-2 in clinical practice [32,33]. Metformin prescriptions should be evaluated taking into account the renal function status of the patients. In fact, metformin is contraindicated in patients with eGFR <30 mL/min/1.73 m^2 whereas the risk-benefit ratio related to treatment should be reassessed when eGFR <45 mL/min/1.73 m^2; however, the same treatment should not be started in patients with eGFR <45 mL/min/1.73 m^2. This recommendation is explained by metformin pharmacokinetics: it is not metabolized in the liver and is almost entirely excreted by kidney [34,35]. For this reason, this drug may accumulate in patients affected by acute or chronic renal injury, thus causing lactic acidosis, which is a rare but serious metabolic adverse effect (43 cases/100,000 patient-years) [35–37]. However, a recent review reported several preclinical and clinical studies that describe the beneficial effect of metformin in slowing CKD development in patients with diabetes [38].

Several studies have shown that the prescription of nephrotoxic drugs is widely used in the clinical practice [39–41], although drugs can cause damage to kidney, both in nephrons and in tubules [42,43]. No correlation was observed between nephrotoxic drug prescriptions and decreased renal function in our study and almost all patients (96.1 %) had a prescription for nephrotoxic drugs. The most used classes of nephrotoxic drugs were PPIs, NSAIDs, and antibiotics. However, the non-correlation with GFR reduction could be attributed to the occasional use of these drugs (for specific treatments) and not to the long-term therapy, thanks to the good attitude of GPs in the management of such patients.

5. Conclusions

The present study improves information on GFR changes in a diabetic population with quite good metabolic control, managed by GPs. The eGFR decline was related with HF and diabetes duration. Additionally, a greater probability of kidney function reduction was

observed in patients who preserved GFR values.

In conclusion, patients with diabetes with additional risk factors related with decreased kidney function, such as HF and early onset of diabetes, should be more carefully observed regardless of GFR values. In particular, even in patients with normal kidney function values, the opportunity to treat with oral glucose lowering agents with "reno-protective" effects, reducing the risk of a progressive decline of GFR, should be considered.

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Institutional Review Board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Messina University Hospital (protocol code 5020 and date of approval June 29th, 2020).

Data availability statement

The data used in this study were obtained from 18 GPs belonging to the Audit & Research Messina Primary Care Group, therefore the generated datasets could not be made publicly available but further requests can be directed to the corresponding author.

CRediT authorship contribution statement

Michelangelo Rottura: Writing – original draft, Formal analysis. **Selene Francesca Anna Drago:** Formal analysis. **Viviana Maria Gianguzzo:** Writing – original draft. **Antonino Molonia:** Formal analysis. **Giovanni Pallio:** Writing – original draft. **Riccardo Scoglio:** Data curation. **Sebastiano Marino:** Data curation. **Angela Alibrandi:** Formal analysis. **Egidio Imbalzano:** Methodology. **Francesco Squadrito:** Writing – review & editing, Supervision, Methodology. **Natasha Irrera:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Vincenzo Arcoraci:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

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.

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