Quality of diabetes mellitus therapy in patients with chronic kidney disease in the real world

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ABSTRACT

Chronic kidney disease (CKD) is very often among diabetic patients. Some oral antidiabetic agents are not recommended in the presence of CKD. Aim of the study was to evaluate the quality of diabetes mellitus (DM) treatment in nephrophatic patients in the real world. A total of 265 subjects with type 2 DM, consecutively admitted to the internal medicine departments of two hospitals in Rome, were recruited. Patients hospitalized for hypoglycemia, decompensated DM, acute kidney failure or worsening nephropathy were excluded. For each patient, the following data were collected: age, gender, estimated glomerular filtration rate (eGFR) using the MDRD (*modification of diet in renal disease*) study equation, type of antidiabetic drug treatment. A total of 265 subjects were studied, 127 male (47.9%) and 138 female (52.1%). The mean age was 77.5 years. The mean of glycemia glycated hemoglobin (HbA1c) value was 57.5 mmol/mol (7.4%). 137 patients (51.7%) were treated with oral antidiabetic agents, 29 (10%) with both oral antidiabetic agents and insulin, 90 (34%) with insulin alone, 8 (3%) with dipeptidyl peptidase-4 inhibitors, 1 (0.4%) with incretin agents plus oral antidiabetic drugs. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) classification of CKD, the sample was divided into 5 groups using eGFR criteria. For each group, mean HbA1c values, type of antidiabetic treatment, appropriateness of therapy according to guidelines and how it may affect the HbA1c levels were considered. Our data show that 30.5% of patients with CKD stage 3-5 is treated with drugs not recommended by current guidelines.

Introduction

Patients affected by diabetes mellitus (DM) are at a high risk to develop chronic kidney disease (CKD). CKD is defined by the presence of structural or functional abnormalities, as persistent proteinuria or decreased glomerular filtration rate, for three months or more. CKD is estimated to affect about one-third of diabetic patients and DM is the leading cause of end-stage renal disease.[1] A recent American study confirmed the high prevalence of CKD in type 2 diabetes mellitus (T2DM), impacting around 40% of this population.[2] An Australian study revealed that 23% of patients affected by T2DM had an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. The authors concluded that about 40% of patients had evidence of CKD.[3] Recent Italian data from RIACE (*renal insufficiency and cardiovascular events*) study documented, in a large cohort of 15,773 Italian subjects with T2DM, CKD was observed in 37.5% of individuals, with a prevalence of stage 1-2 of 18.7% and stage 3-5 of 17.8%.[4] Therapeutic options for patients with renal failure are limited because a reduced GFR results in the accumulation of insulin and oral antidiabetic agents and an increased risk of hypoglycemia. There are no significant restrictions on the use of drugs in CKD stage 1 and 2, while in moderate and severe renal disease (stage 3-5) some antidiabetic agents are not recommended and others need dose adjustment.[5-11] The objective of the present study is to evaluate the appropriateness of DM treatment in patients with CKD in the real world.

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Key words: Diabetes mellitus; chronic kidney disease; hypoglycemic agents; elderly.

Conflict of interest: the authors declare no potential conflict of interest.

Award: *Premio Ricerca FADOI Lazio 2015* - 2nd place.

Received for publication: 9 April 2016.
Accepted for publication: 11 April 2016.

Italian Journal of Medicine 2017; 11:48-51
doi:10.4081/itjm.2017.726

Materials and Methods

The study included 265 diabetic patients consecutively admitted to internal medicine department of two

hospitals in Rome between January 2013 and May 2014. Patients hospitalized for hypoglycemia, decompensated DM, acute kidney failure or progressive kidney disease were excluded. An interviewer-a dministered questionnaire was used to gather the following data: age, gender, schooling, duration of diabetes, type of DM treatment (oral antidiabetics agents, insulin or oral antidiabetic agents plus insulin) and glycemia glycated hemoglobin (HbA1c), creatinine value on admission. All patients underwent eGFR measurement by the the MDRD (*modification of diet in renal disease*) study equation.

Results

A total of 265 subjects were studied, 127 male (47.9%) and 138 female (52.1%). The mean age was 77.5 years. The mean HbA1c value was 57.5 mmol/mol (7.4%). 137 patients (51.7%) were treated with oral antidiabetic agents, 29 (10.9%) with oral antidiabetic agents in combination with insulin, 90 (34%) with insulin alone, 8 (3%) with dipeptidyl peptidase-4 inhibitors (DPP-4), 1 (0.4%) with incretin agents plus oral antidiabetic drugs. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) classification of CKD, the sample was divided into 5 groups using eGFR criteria (Table 1).[5]

Stage 1 CKD group: 33 patients, mean age 68.5 years, mean HbA1c value 61.7 mmol/mol (HbA1c 7.8%). Stage 2 CKD group: 68 patients, mean age 73.6 years, mean HbA1c value 59.7 mmol/mol (HBA1c 7.6%). Stage 3 CKD group: 92 patients, mean age 80.3 years, mean HbA1c value 58.4 mmol/mol (HbA1c 7.5%). Stage 4 CKD group: 55 patients, mean age 82.1 years, mean HbA1c value 52.9 mmol/mol (HbA1c 7%). Stage 5 CKD group: 17 patients, mean age 79.2 years, mean HbA1c value 51.6 mmol/mol (HbA1c 6.9%) (Table 2).

Stage 1-2 CKD subjects were 101, 52 (51.5%) were treated with oral antidiabetic agents, 15 (14.9%) with insulin in combination with oral antidiabetic drugs, 32 (31.7%) with insulin alone, 2 (1.9%) with DPP-4 inhibitors.

Of those treated with oral antidiabetic agents, 53 took metformin, 1 pioglitazone, 11 glibenclamide, 5 glimepiride, 9 repaglinide.

Stage 3-5 CKD patients were 164, 85 (51.5%) were in treatment with oral antidiabetic agents, 14 (8.5%) with insulin and oral antidiabetic drugs, 58 (35.4%) with insulin alone, 6 (3.7%) with DPP-4 inhibitors alone, 1 (0.6%) with oral antidiabetic agents and DDP-4 inhibitors.

In those treated with oral antidiabetic agents, 51 used metformin, 21 glibenclamide, 5 glimepiride, 7 DDP-4 inhibitors, 32 repaglinide and 3 acarbose (Fig-

Table 1. Stages of chronic kidney disease.

Stage	Description	eGFR mL/min/1.73 m^2
1	Normal or increased GFR, with other evidence of kidney damage	>90
2	Slight decrease in GFR, with other evidence of kidney damage	60-89
3	Moderate decrease in GFR, with or without other evidence of kidney damage	30-59
4	Severe decrease in GFR, with or without other evidence of kidney damage	15-29
5	Established renal failure	<15

eGFR, estimated glomerular filtration rate. *Modified from Eckardt* et al., *2009.*[5]

Table 2. Characteristics of patients with chronic kidney disease.

CKD stage	Total	Male	Female	Medium age	Medium HbA1c
1	33	14	19	68.5	61.7 mmol/mol (7.8%)
2	68	40	28	73.6	59.7 mmol/mol (7.7%)
3	92	41	51	80.3	58.4 mmol/mol (7.5%)
4	55	23	32	82.1	52.9 mmol/mol (7.0%)
5	17	9	8	79.2	51.6 mmol/mol (6.9%)
Total	265	127	138	77.5	57.5 mmol/mol (7.4%)

CKD, chronic kidney disease; HbA1c, glycemia glycated hemoglobin.

ure 1). A total of 50 (30.5%) patients with CKD stage 3-5 was treated with hypoglycemic agents not recommended by guidelines.

Discussion and Conclusions

This observational study describes the quality of metabolic compensation and the distribution of glucose lowering drugs in a cohort of 265 diabetic subjects with CKD, consecutively admitted to internal medicine departments of two hospitals in Rome between January 2013 and May 2014. This real-world study demonstrated a good metabolic compensation in our cohort (mean HbA1c value 57 mmol/mol, 7.4%). This finding is similar to the one documented in the population of the National Health and Nutrition Examination Survey (NHANES).[12] Moreover, a progressive decrease in HbA1c value in the advanced stages of CKD was documented. In particular, HbA1c levels of diabetic patients with CKD stage 4 (HbA1c 52.9 mmol/mol, 7.0%) and above all, stage 5 (51.6 mmol/mol, 6.9%) are probably too low considering the age of the study sample. Actually, current recommendations for diabetes management endorse higher glycemic targets for older patients with multiple comorbidities.[9-11] The reason for higher glycemic targets in these persons is the evidence that intensive glycemic control strategies markedly increase the risk of hypoglycemia.[13-15] Recent reports suggest that a substantial number of older adults with diabetes were potentially overtreated.[12,16] The potential overtreatment is defined as an HbA1c level of less than 7%. Our study suggests that diabetic subjects with advanced CKD may be those at higher risk of overtreatment. Consequently, these patients may be likely to experience harms from treatment, such as hypoglycemia.

CKD is a common complication of diabetes; it contributes to clinical complexity of diabetes management. Renal impairment limits the use of certain hypoglycemic agents because it increases the risk of serious drug adverse effects. In stage CKD 1-2 there is no limitation in the choice of hypoglycemic therapy nor any dose adjustment. In CKD stage 3-5 some drugs are not recommended.[5-11] Our study found that a consistent number of stage 3-5 patients took a therapy not recommended by guidelines. Actually, 17 patients with CKD stage 3 took glibenclamide, 4 patients with CDK stage 4 took glibenclamide + metformin, 8 patients metformin, 2 patients metformin + repaglinide, 12 patients repaglinide, 4 patients affected by end stage renal disease (stage 5) used metformin, 1 glimepride, 2 repaglinide. Since current recommendations for diabetes management do not recommend the use of glibenclamide with eGFR <60 mL/min, and the use of glimeperide, metformin and repaglinide with eGFR <30 mL/min a total of 50 patients (30.5%) with CKD stage 3-5 resulted in treatment with hypoglycemic medications not recommended by the current guidelines. The administration of metformin was not considered inappropriate in patients with CKD stage 3, according to the consensus report on antidiabetic therapy in older adults of the American Diabetes Association and the American Geriatric Society that suggests metformin in reduced dosage for patients with eGFR value between 30 and 60 mL/min and considers eGFR values <30 mL/min as contraindication.[10]

This real-world study showed that more than one third of patients with CKD stage 3-5 in treatment with

Drugs / CKD stage	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5
Metformin	14	39	33	14	4
Glibenclamide	3	8	17	4	0
Glimepiride	1	4	3	1	1
Repaglinide	5	4	11	19	2
Pioglidazone	1	0	0	0	0
Acarbose	0	0	3	0	0
DPP-4 inhibitors	0	2	1	4	2
Insulin	12	18	55	21	9

Appropriate use Dose reduction requested To be avoided

Figure 1. Drugs distribution and appropriate use in different chronic kidney disease (CKD) stage. DPP-4, dipeptidyl peptidase-4 inhibitors.

hypoglycemic agents received a non-recommended treatment. This finding confirms the one of other researches. A recent survey in France to investigate therapeutics strategies of general practitioners in the management of T2DM patients with CKD showed that more than two-thirds of patients were treated with glucose lowering agents which were either contraindicated or nonrecommended for CKD.[17] Another work performed in USA studied the pattern of oral antidiabetic drug use and their concordance with the National Kidney Foundation guideline. A little over a quarter of the patients received at least one drug, which was not recommended.[18] Moreover, our study documented that the most frequently used oral antidiabetic agents in DM treatment are metformin, glibenclamide, repaglinide and glimperide. The hypoglycemic agent that has been inappropriately prescribed most frequently was glibenclamide. This finding confirms the one of a research performed in Germany which documented that glibenclamide was commonly used despite its classification as potentially inappropriate medication in older adults.[19]

There were some limitations in this study. Firstly, patients were evaluated at admission to hospital. Thus, the existing clinic condition that led to recovery may have made manifest or have made worse renal impairment, resulting in overestimation of the number of patients treated inappropriately. Moreover, the high mean age, the comorbidities and the subsequent polytherapy of the examined sample may favor the occurrence of drug adverse effects, including further loss of renal function. Nevertheless, the percentage of diabetic patients with CKD who takes a non-recommended therapy is still substantial.

In summary, our data demonstrate that about one third of diabetic patients with CKD stage 3-5 take an antidiabetic drug treatment not recommended by guidelines. The results showed a progressive reduction in HbA1c levels in the advanced stages of kidney disease. Patients in CKD stage 5 are exposed to the potential risk of overtreatment.

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