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Glycemic control according to glomerular filtration rate in patients with type 2 diabetes and overt nephropathy: A prospective observational study

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ABSTRACT

Background and Objective: Type 2 diabetes (T2D) and chronic kidney disease (CKD) are closely linked. This study aimed to describe and analyze the relations between renal function and glycemic control in T2D patients with overt nephropathy.

Patients and methods: Data were collected from a French observational prospective multicenter study. Patients included were adults with T2D, clinical proteinuria and an estimated glomerular filtration rate (eGFR) over 15 mL/min/1.73 m^2. Baseline data and glycemic control after a one-year follow-up are presented here.

Results: Data from 986 adult patients were analyzed. Mean age was 70 years. Mean eGFR was 42 mL/min/1.73 m^2, 66% of patients had proteinuria above 1 g/day. HbA1c was higher in patients with lower eGFR in a model adjusted to age, gender, body mass index, hemoglobin level and erythropoietin use. Statistical significance was lost when stepwise multivariate analysis took into account the type of pharmacological treatment used to treat hyperglycemia.The type of antidiabetic agents differed across eGFR strata. Below 60 mL/min/1.73 m^2,

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Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CRF, case-report form; ENTRED, Echantillon National Témoin Représentatif des Personnes Diabétiques; ESA, erythropoiesis stimulating agent; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HBPM, home blood pressure monitoring; MDRD, modification of diet in renal disease; OAD, oral antidiabetic agents; OR, odd-ratio; RAS, renin angiotensin system; SD, standard deviation.

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the use of metformin declined while the use of insulin increased.After one year of follow up, 35% of patients had persistently poor or worsened glycemic control (HbA1c > 8%). The only covariate independently associated with this characteristic was the duration of insulin therapy.

Conclusion: In patients with T2D and overt nephropathy, the observed correlation of low eGFR with high HbA1c was not predicted by eGFR. Our data rather underscore a different use of antidiabetic treatments in patients with advanced renal dysfunction, and the difficulty to improve glycemic control in patients with long standing insulin therapy.

1. Introduction

Type 2 diabetes mellitus and chronic kidney disease (CKD) are closely linked. On the one hand, type 2 diabetes mellitus is a major cause of CKD. On the other hand, insulin resistance is common in patients with mild-to-moderate chronic kidney dysfunction [1] and it is well documented that aggravation of non-diabetic renal disease may give rise to hyperglycemia, a strong indicator of morbidity and mortality. Loss of glomerular filtration (GFR) may thus alter glycemic regulation in either diabetic or non-diabetic renal disease. Loss of GFR may in contrast be associated to better glycemic control in diabetic patients with advanced renal failure, with several potential mechanisms involved, such as reduced renal degradation of insulin, reduced renal neoglucogenesis, and reduced food intake [2]. Loss of GFR also modifies the metabolism of drugs used to treat hyperglycemia. The exposition length to drugs and their metabolites is increased, with potential iatrogenic side effects. Among them, increasing attention is being given to hypoglycemia [3,4].

Physicians are well aware of the complexity of glycemic management of diabetes in patients with impaired renal function. Additionally, the benefits of antidiabetic therapy in preventing renal and cardiovascular complications have not been formally proven in patients with CKD, and specific guidelines to direct glycemic therapy are lacking in this specific population.

There is need for a better understanding of the complex interrelation between renal function and glycemic control. In the present study, we describe the baseline characteristics of the ''ALICE-Protect'' study population, a prospective observational multicenter study designed to assess management of patients with type 2 diabetes mellitus and nephropathy, all included by nephrologists, in real life conditions in France. We also describe the therapeutic management of diabetes according to renal function, the determinants of glycemic control across various GFR strata and the evolution of glycemic control after one-year of follow-up.

2. Materials and methods

2.1. Study population and setting

The ALICE-protect cohort, planned to include 1200 patients, was formed between January 2010 and February 2011. All known nephrologists throughout France ($n = 1118$) were invited to participate; 153 accepted and actively recruited patients. These nephrologists were representative of the practices of nephrology in France, including public hospitals, for profit and non-profit private hospitals. Each physician was asked to include up to 15 consecutive patients meeting the inclusion criteria.

Inclusion criteria were (i) age over 18 years, (ii) type 2 diabetes mellitus, (iii) clinical proteinuria, defined by 24-h proteinuria $\geq$0.5 g per day or urinary protein/creatinine ratio $\geq$50 mg/mmol ($\geq$500 mg/g) or urinary albumin/creatinine ratio $\geq$30 mg/mmol ($\geq$300 mg/g), and (iv) an estimated glomerular filtration rate (eGFR by MDRD formula) over 15 mL/min/1.73 m^2. Pregnant women, patients with renal transplantation or those already included in a clinical study were not included.

The planned follow-up for the whole population is 2 years, up to June 2013, with one planned visit per year $\pm$4 months.

The main goal of the ALICE-protect study was to evaluate the percentage of patients with type 2 diabetes mellitus and nephropathy reaching blood pressure (BP < 130/80 mmHg) and proteinuria (<0.5 g/day) targets after a 2-year follow-up in real-life conditions; secondary endpoints were the occurrence of renal and cardiovascular complications in real-life conditions.

2.2. Data collection

No specific assessment was requested for the study. The following data were recorded from the patients' medical records and on the basis of the interview performed during the inclusion visit: demographics, duration of diabetes, associated cardiovascular risk factors and major diabetes complications; symptoms which could be evocative of neuropathy, lower limb arteriopathy or orthostatic hypotension; most recent laboratory parameters available and current treatments (antihypertensive drugs, erythropoiesis stimulating agents [ESA], lipid-lowering agents, anti-platelet agents and antidiabetic treatments specified as metformin, insulin or other oral antidiabetic agents). Treatments were recorded by class, without specification of the pharmaceutical name with the exception of aliskiren which is the only direct renin inhibitor available on the market. For all renin angiotensin system (RAS) blockers [aliskiren, angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs)], physicians were asked to indicate by means of a specific table provided by the sponsor whether dosages were low, medium, high or very high. Each patient was given a physical examination including BP measurement in a sitting position after a 5-minute rest. Results of recent ambulatory BP monitoring