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Renal Dysfunction as Assessed by MDRD and Cystatin-C in a Belgian Cohort of Type 2 Diabetic Patients Followed in an Outpatient Clinic

Disfunção Renal Avaliada pela MDRD e a Cistatina-C numa Coorte Belga e Pacientes com Diabetes Tipo 2 Seguidos em Ambulatório

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Abstract

Chronic kidney disease is a frequent complication in type 2 diabetes. We evaluated prospectively the prevalence of stages 3-5 disease on the basis of GFR as well as abnormal cystatin-C levels in a cohort of 200 patients followed in an outpatient clinic. 22% of our subjects had low GFR levels and 31% abnormal cystatin-C values. These figures confirm that a screening of renal (dys)function in a diabetic population is mandatory.

Resumo

A doença renal crónica é uma complicação frequente da diabetes tipo 2. Avaliámos prospectivamente a prevalência de doença renal crónica nos estádios 3-5 com base na taxa de filtração glomerular, bem como nos níveis anormais de cistatina-C, numa coorte de 200 pacientes seguidos no ambulatório. Desses pacientes, 22% tinham níveis de taxa de filtração glomerular baixos e 31% valores anormais de cistatina-C. Estas percentagens confirmam que na população diabética o rastreio da (dis)função renal é obrigatório.

> INTRODUCTION

Chronic kidney disease (CKD) is a common complication in patients with type 2 diabetes [1]. It is usually defined as microalbuminuria (stages 1-2) or as a creatinine-based estimated glomerular filtration rate (GFR) of less than 60 ml/min/1,73m^2 (stages 3-5) [2]. Another currently available and validated tool to detect CKD is an increased serum cystatin-C [3-6].

CKD is associated with an increased risk of adverse outcomes including death, cardiovascular events and/or the development of end-stage renal disease [1,7]. Moreover, hyperglycemia is usually difficult to manage and to normalize in renal impairment, at least in stages 3-5, due to the relatively limited therapeutic options.

For those reasons, clinicians are particularly sensitized to the development or progression of CKD in their diabetic subjects.

The purpose of this study is to evaluate the prevalence of stages 3-5 CKD on the basis of GFR, as well as renal impairment assessed by abnormal cystatin-C levels in a cohort of type 2 diabetic individuals regularly followed in the outpatient clinic of a university center in Belgium.

> PATIENTS AND METHODS

200 consecutive caucasian patients (116 males; 84 females) with type 2 diabetes were included in this prospective survey. The study visit was performed between January 2012 and July 2012 at the outpatient clinic of the University Hospital St-Luc (Brussels). Patients hospitalized for treatment of diabetes and/or evaluation of chronic complications were excluded from the study as were subjects with type 1 diabetes or secondary diabetes, or subjects with a non-diabetic renal disease.

As indicated in Table 1, age and duration of diabetes for

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Table I - Clinical characteristics.

	Total cohort (n=200)	Males (n=116)	Females (n=84)
Age (years)	63 ± 12	61 ± 12	65 ± 13
Duration of diabetes (years)	12 ± 9	10 ± 8	14 ± 10
BMI (kg/m^2)	30,9 ± 5,5	30,6 ± 5,2	31,4 ± 5,9
Blood pressure (mmHg)			
Systolic	133 ± 17	133 ± 15	133 ± 19
Diastolic	78 ± 10	78 ± 10	78 ± 10
HbA1c (%)	7,9 ± 1,4	7,8 ± 1,3	8,1 ± 1,5

Table II - Biological results.

	Total cohort (n=200)	Males (n=116)	Females (n=84)	
Creatinine (mg/dl)	0,9 ± 0,3	1,0 ± 0,3	0,8 ± 0,2	
GFR (MDRD) (ml/min/1,73m^2)	79 ± 24	82 ± 22	76 ± 28	NS
Cystatin-C (mg/l)	0,89 ± 0,28	0,90 ± 0,31	0,90 ± 0,25	NS
Microalbuminuria (nbr of patients)	73	42	31	NS
Macroproteinuria (nbr of patients)	13	6	7	NS

the total cohort were 63 ± 12 and 12 ± 9 years, respectively (mean +/- 1 SD). Female patients were older than males (p = 0,002) and tended to have longer duration of diabetes. Body mass index (BMI) was 30,9 ± 5,5 kg/m^2. Systolic and diastolic blood pressure levels, as indicated in Table 1, were comparable in males and females. Retinopathy, as assessed by fluoangiography, was present in 45 individuals. 54% of patients were treated with insulin injections administrated alone or in combination with oral antihyperglycemic agents. Overall, metformin was administrated to 73% of patients, sulfonylureas to 31% and DPP4-inhibitors to 6%. GLP-1 analogues were administrated in 17 % of individuals. Antihypertensive therapy, mainly ACE-inhibitors or sartans, was administrated to 79% of the patients at the time of the study visit.
Measurement of glycated haemoglobin (HbA1c) using high-pressure liquid chromatography (HPLC) was standardized according of the national glycohemoglobin standardization program [8]. Plasma creatinine levels were measured conventionally on Olympus AU 2700 analyser from Beckman Coulter (USA).
GFR was measured using the Modification of Diet in Renal Disease (MDRD) equation [9]. Cystatin-C determination was obtained (in 83 patients) by a particle-enhanced nephelometric method on BNII (Siemens, Germany). Reference values in patients less than 60 years old are 0,54 – 0,94 mg/l in males and 0,48 – 0,82 mg/l in females. Normal values were 0,63 – 1,03 mg/l in subjects aged ≥ 60 years [3]. Microalbuminuria was determined by a nephelometric method (Siemens, Germany).
Data are presented as means ± 1 SD. The significance of differences between means was assessed by Student's t-test. Correlation between variables used the Pearson correlation test. Results were considered significant at p < 0,05.

> RESULTS

For the total group, mean HbA1c was 7,9 ± 1,4% (63 ± 11 mmol/mol) (Table 2).
64 patients (41 M; 23 F) had an HbA1c level ≤ 7% (53 mmol/mol) and 94 a value ≤ 7,5% (58 mmol/mol). Mean plasma creatinine was 0,9 mg/dl (Table 2). Estimated GFR for the total cohort was 79 ± 24 ml/min/1,73m^2 (M *vs* F: NS). We observed that GFR was lower than 60 ml/min/1,73m^2 in 44 patients (17 M; 27 F) (22%). Only one subject had a GFR value lower than 30 ml/min/1,73m^2. Mean serum cystatin-C level was 0,89 ± 0,28 mg/l (M *vs* F: NS). Elevated cystatin-C levels were observed in 26 patients (15 M; 11 F) (31%).
A significant correlation was observed between GFR (as expressed by MDRD) and cystatin-C (r=0,629; p < 0,001) (Figure 1). Microalbuminuria was found in 73 subjects (42 M; 31 F) (NS) and macroproteinuria in 13 individuals (6 M; 7 F) (NS).

> DISCUSSION

To our knowledge, the present study is the first to report the prevalence of renal impairment in a belgian outpatient type 2 diabetic population. We observed a global prevalence of 22% of CKD 3-5, with all but one subject characterized by a GFR between 30 and 60 ml/min/1,73m^2 (stage 3). The prevalence of CKD 4-5 could however be underestimated since we selected only non-hospitalized diabetic subjects at the time of their visit at the outpatient clinic. This prevalence in Belgium is close to previous reports in Europe and USA. A substantial number of data indicate indeed CKD 3-5 prevalence between 20 and 23% [10-13].
We observed a correlation between GFR and serum cystatin-C. Cystatin-C is a protein with constant production rate that undergoes glomerular filtration [3-6]. Using cys-

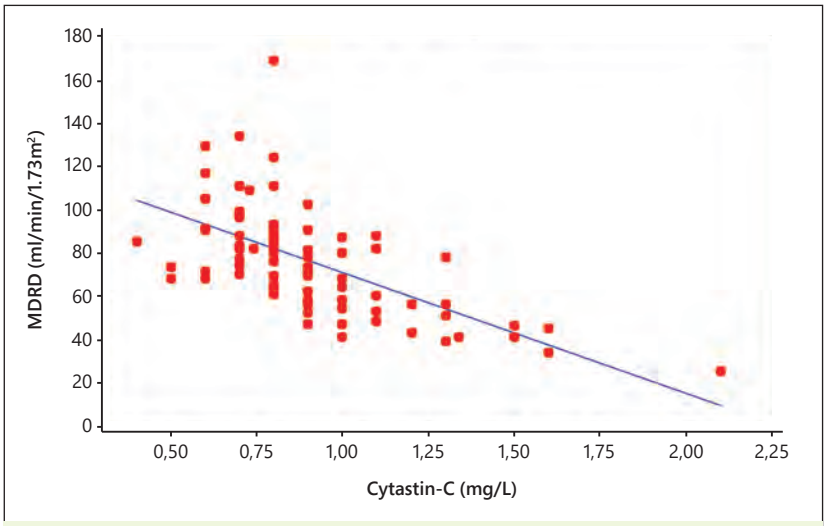

Figura 1 - Correlation between MDRD and cystatin-C levels.

tatin-C dosage, the prevalence of renal impairment in our patients increased up to 31%. This could be due to the fact that cystatin-C is a serum biomarker, which provides GFR estimates less affected by age, race of muscle than creatinine [3,5]. Other authors confirm that cystatin-C discriminates better among populations of type 1 and 2 diabetic subjects with regards to their estimated GFR when compared with conventional creatinine measurement [4]. In this line, Inber et al reported however that a combined creatinine – cystatin-C equation performed even better than equation based on either of those markers alone [6]. Cystatin-C is also a stronger predictor of the risk of cardiovascular morbidity and mortality, in particular in elderly persons than creatinine [1,4]. Therefore, the use of serum cystatin-C as a diagnostic test for CKD in general is of interest [15]. Bias in our study however could be that cystatin-C was measured only in 40% of the total patient's cohort.

In parallel, the prevalence of microalbuminuria, another predictor of progression to end-stage renal disease or death [16] in our patients was close to that reported by Parving *et al* [11]. Macroproteinuria was lower, probably due to the clinical profile of the study population.

Finally, our data also show that glycemic control in our patients remains globally unsatisfactory, since more than 50% of our subjects had an HbA1c higher than 7,5% (58 mmol/mol). A more individualised glycemic optimization approach, as indicated in the recent ADA – EASD recommendations should improve overall control [17].

In conclusion, we observed in this belgian population a CKD prevalence between 22% and 31% according to the used biomarker. Future studies are needed in order to define the final place of serum cystatin-C as a routine biomarker of renal impairment.

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