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Editorial

THE DIABETIC RENAL DISEASE – NEW INSIGHTS IN 2012

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Recently, the KDIGO Controversies Conference on Diabetic Kidney Disease (New Delhi, India, March 2012) conference reports have been published. KDIGO (Kidney Disease-Improving Global Outcomes) is a global non-profit foundation dedicated to improving the care and outcomes of kidney disease patients worldwide.

Several important topics have been debated and some changes are now intended to be introduced in the new clinical practice nephrology guidelines. Other relevant papers dedicated to diabetic renal disease have been also published in recent years.

New epidemiological data have shown that an important increase in the prevalence of diabetic renal disease (DRD) has been registered in the USA [1]: 39.6% of known diabetic patients are diagnosed with renal impairment (27% being in stage 2 CKD or even more advanced); in addition, 41.7% of the adults with previously undiagnosed diabetes mellitus also have chronic kidney disease (CKD) at diagnosis and 35% should be included in stage 2 CKD or more advanced.

In patients with type 2 diabetes mellitus treated in primary care consults in Spain, 27.9% presented some degree of CKD as follows: 3.5% with stage 1; 6.4% with stage 2; 16.8% with stage 3 and 1.2% with stages 4 and 5 [2].

A recent multicenter study from Germany has shown that about 9.4% of chronic dialyzed patients have been discovered with undiagnosed diabetes mellitus and other 31% were included in high risk categories for type 2 diabetes mellitus (T2DM): Impaired Fasting Glycemia:12.3% and Impaired Glucose Tolerance: 18.9%. No difference in mortality rates has been detected between dialyzed patients with diabetes mellitus (DM) as a primary renal disease and those with DM considered as a co-morbid condition [3].

Looking for the most relevant associations, blood pressure (BP) remains one of the best predictors. Between the clinical parameters of BP and the relative risk for increase in the DRD progression rate, the nocturnal non-dipping pattern appears to be related to a significant increase in urinary albumin excretion rates (UAER) in T2DM patients [4]. An association was also found between the 24 hours pulse pressure (PP) values and the progression rates of DRD [5].

Other new risk factors for a more rapid decline of the kidney function in DM patients

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like hyperuricemia [6] and serum phosphates [7] have been identified in the last years.

A characteristic of the DRD evolution in elderly T2DM patients is their high risk for acute kidney injury (AKI), which usually develops secondary to chronic hyperglycemia; in a recent paper, Ishani et al. [8] has shown that in T2DM patients with established DRD the relative risk for ESRD after an AKI episode was significantly higher, than before the AKI episode (RR: 2.24; 95%CI: 1.9-5.2).

Albuminuria versus estimated glomerular filtration rate (eGFR) as markers of DRD progression

Albuminuria (urinary albumin excretion rate, UAER) as a marker of DRD progression implies high variability, low specificity and the possibility of spontaneous regression. On the other hand, the estimated Glomerular Filtration Rate (eGFR) is characterized by a low variability, high specificity and a reduced probability of spontaneous regression, which makes it the best index for kidney function.

In a paper published by Perkins et al. [9], the reliability of UAER as a marker of progressive renal function decline (>3.3%/year) in a cohort of T1DM patients was analyzed. The patients from the microalbuminuric group were divided into two categories according to the 4-year progression of the UAER (progressors to macroalbuminuria versus non-progressors). The results have demonstrated a robust correlation between all the evolutive steps of the UAER and the risk for progressive renal function decline.

In T2DM patients, the pattern of the association of UAER progression with the renal function progressive decline is somehow different [10]: renal function decline is strongly dependent on the progression from micro- to macroalbuminuria (clinical proteinuria), but not from normo- to microalbuminuria.

The intensive multifactorial therapy intervention in T2DM patients significantly decreased UAER at 7.8 years (58 vs. 99 mg/24h; $p < 0.01$) but had no effect on the GFR decline. Yet, the lowest GFR decline rate in the Steno 2 cohort was recorded in patients with a remission of UAER from micro- to normoalbuminuria [11].

In conclusion:

– Both albuminuria and eGFR should be assessed as markers of DRD progression; they should be considered as having complementary roles in staging and stratifying the vital and progression risk in DRD patients;

– A decline of eGFR is most frequently accompanied by an increase in albuminuria, but in some DM patients a non-albuminuric pattern of DRD progression towards ESRD was also described;

– Risk for progression to ESRD, especially for T2DM patients, is usually strongly dependent on progression to macroalbuminuria.

Albuminuria as a treatment target

Probably the most frequent asked albuminuria question raised in the last years is if a high UAER in a DM patient is a therapeutic target or only a biomarker (the „innocent bystander" theory). This controversy should be split today into two different arms: albuminuria as a treatment strategy determinant and albuminuria as a prediction parameter for treatment efficacy.

It is advisable now to consider UAER as an essential criteria for allocating a DM

patient to a treatment strategy: primary or secondary prevention; intensified blood glucose versus intensified blood pressure (BP) intervention, etc. The type of diabetes mellitus should also modulate these options.

Reducing the frequency of micro- to macroalbuminuria progression through intensive glycemic control (primary prevention) appears to be the best strategy to reduce the risk of kidney failure and cardiovascular morbidity/mortality for microalbuminuric T1DM (DCCT/EDIC) [12] as for T2DM patients (UKPDS, ADVANCE and UKPDS follow-up) [13,14]. In T1DM patients, the intensified BP control strategy neither prevented the transition from micro- to macroalbuminuria nor reduced the risk for kidney failure or cardiovascular events or death.

Contrariwise, in T2DM patients, the same BP intensive control treatment strategy was demonstrated effective in preventing the progression from micro- to macroalbuminuria (UKPDS) and reduce the cardiovascular risk (HOPE trial) [15], but not the risk for ESRD.

In conclusion:

– Primary prevention of microalbuminuria and/or progression to macroalbuminuria is a valuable target for both strict blood glucose control and BP control, especially in T2DM patients;

– Secondary interventions on blood glucose control and BP control also in micro- and macroalbuminuric patients are both valuable for their final renal and cardiovascular outcomes;

– Variations in micro- and macroalbuminuria status as response to different treatment strategies are useful tools;

– The lower the blood glucose and BP and the higher the angiotensin receptor/converting enzyme inhibitors doses, the better for the final renal and possible cardiovascular outcomes in patients with DM.

Arterial hypertension in DM patients with renal involvement

The dual nature of the relationship between the kidney and the BP in terms of "kidney culprit" versus "kidney victim" should be translated nowadays for DM patients. In T1DM patients, the first is more probable since diabetic nephropathy is the primary glomerular disease (signaled by increased UAER) which induces hypertension as a consequence. On the other hand, in T2DM patients the kidney is usually a „victim" of the essential hypertension which affects target organs such as: heart (left ventricle hypertrophy) and kidney (high UAER).

As it was previously shown, the intensified BP control as a primary prevention strategy has no notable effect on cardiovascular risk in T1DM patients, but the results were good in T2DM in which the prevention of the micro- to macroalbuminuria progression reduces the cardiovascular outcomes. The same strategy in secondary prevention revealed excellent results on cardiovascular outcomes in long term follow up of T1DM patients (DCCT/EDIC); the results on cardiovascular mortality outcome have to be published soon.

The *American Diabetes Association* Clinical Practice Recommendations 2013 stated that the BP goal in DM patients must be under 140/80 mmHg, and less than 130/80 mmHg in younger patients and in those without severe co-morbidities [16].

The great majority of DRD patients (more than 75%) will need two or more antihypertensive drugs to achieve the blood pressure targets. The second drug should be introduced if the BP is 20/10 mmHg above the target (JNC7), especially if the patient is already on a low sodium diet.

The KDIGO Controversies Conference on Diabetic Kidney Disease stated that because of the dramatic increase in the number of individuals developing diabetes, it is important to develop cost-effective strategies at every step: prevention of obesity; screening for and prevention of diabetes in an at-risk population; glycemic control once diabetes develops; blood pressure control once hypertension develops; screening for diabetic CKD; use of renin angiotensin aldosterone system (RAAS) inhibition/blockade in those with diabetic CKD; and control of other cardiovascular risk factors such as management of LDL cholesterol.

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