MANAGEMENT OF HYPERTENSION IN DIABETIC PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Diabetes mellitus and hypertension are the most common causes of end-stage renal disease. Blood pressure goals in patients with diabetic kidney disease are <130/80 mmHg. The first line therapy for hypertension in these patients are the angiotensin-converting enzyme inhibitors and/or the angiotensin II receptor blockers. These drugs delay the onset of microalbuminuria, retard progression from microalbuminuria to macroalbuminuria, reduce the urinary albumin-creatinine ratio and improve glomerular filtration rate.

key words*: diabetes mellitus, hypertension, diabetic kidney disease*

1. Introduction

Chronic kidney disease (CKD) is defined as a kidney damage or/and decreased kidney function (decrease of eGFR-estimated glomerular filtration rate) for ≥3 months [1]. The presence of kidney damage may be evidenced by increased urinary albumin and/or protein excretion rate, pathological changes of urine sediment and urine chemistries or by abnormalities of imaging studies [1].

The prevalence of CKD in general population is 14-16%. The most common causes of end-stage renal disease (ESRD) in the Western world are diabetes mellitus (DM) and hypertension [2].

CKD can be found in up to 23-25% of patients with DM. Moderate to severe CKD is estimated to be found in 15-23% of patients with DM [2]. DM is the primary cause of kidney failure, and the diabetic patients represent 45% (more than 50% in the USA) of those who receive dialysis therapy.

2. Clinical diagnosis of diabetic kidney disease

CKD considered secondary to DM has been termed "diabetic **nephropathy**" [3]. The Diabetes and Chronic Kidney Disease work group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) suggested that CKD considered to be caused by DM should be named "diabetic kidney disease (DKD)" and the term "diabetic **nephropathy**" should be reserved for kidney disease attributed to DM with histopathological changes, demonstrated by renal biopsy [4].

The clinical diagnosis of DKD is, mainly, based on detection of albuminuria:

– microalbuminuria is defined as an albumin-creatinine ratio (ACR) of 30-300 mg/g from a spot urine collection, urinary albumin excretion (UAE) 30-300 mg/24 hours in a 24-hour urine collection, or 20-200 μg/min in a timed urine collection;
– macroalbuminuria is defined as an ACR >300 mg/g from a spot urine collection, UAE > 300 mg/24 hours in a 24-hour urine collection, or >200 μg/min in a timed urine collection [4].

For initial screening of DKD, measurement of albuminuria from a spot urine is recommended because the ACR by spot urine sample has demonstrated excellent correlation with the 24-hour urine albumin measurements.

If the determination of albuminuria can not be performed at diagnosis, we can measure proteinuria:

– microproteinuria is defined by a value between 300- 500 mg/24 hours;
– macroproteinuria is defined by a value higher than 500 mg/24 hours.

The interventions which proved to prevent the onset or attenuate the progression of DKD are: glycemic and blood pressure (BP) control [5,6], specific blockage of the renin-angiotensin-aldosteron system (RAAS), with either angiotensin-converting enzyme inhibitors (ACEI) [7,8] or angiotensin II receptor blockers (ARB) [7,9,10], and lipid-lowering therapy, especially statins and fibrates.

3. Management of hypertension

3.1. Background

Hypertension is an independent risk factor for cardiovascular disease (CVD) and CKD. In type 1 DM, hypertension is more often the complication DKD, while in type 2 DM it usually coexists with other cardiometabolic risk factors [11].

Hypertension is commonly found in patients with DKD, its prevalence is estimated to be from 30 to 96%, with higher prevalence in patients with albuminuria [4]. Uncontrolled hypertension determine a higher risk of cardiovascular events, including death, increasing proteinuria and progression of kidney disease [12].

The goals of antihypertensive therapy in patients with CKD are to lower BP, reduce CVD risk and slow the progression of CKD [11,13,14].

3.2. Blood pressure targets

In individuals with DM, epidemiologic analyses show that BP over 115/75 mmHg is associated with increased cardiovascular event rates and mortality [15]. The presence of microalbuminuria or microproteinuria requires more aggressive treatment to achieve the recommended BP goals.

Patients with microalbuminuria have higher BP levels than patients with normal albumin excretion. Patients with absent nocturnal dipping of BP had higher levels of microalbuminuria than those with a normal dipping pattern [16].

Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering BP less than 140 mmHg systolic and 80

mmHg diastolic in individuals with DM [17,18].

*In **normoalbuminuric*** **diabetic patients, the t**reatment of hypertension reduces the risk of cardiovascular and microvascular events [14]. In the HOT study, a reduction of diastolic BP with 4 mmHg was followed by a 50% reduction in the risk of cardiovascular events in diabetic patients [18]. In the UKPDS, the reduction of systolic BP, from 154 to 144 mmHg, reduced the risk for the development of microalbuminuria by 29% [6].

Microalbuminuria is an indicator of endothelial dysfunction and an independent marker for cardiovascular morbidity and mortality in individuals with and without DM [13]. In microalbuminuric type 1 and type 2 DM patients the treatment of hypertension, regardless of the agent used, produced a beneficial effect on albuminuria [19].

In proteinuric type 1 diabetic patients, the treatment of hypertension reduced albuminuria and the rate of GFR decline.

BP targets for patients with DM are lower than those for patients without DM [15]. BP goals are <130/80 mmHg in diabetic patients in general, and <125/75 mmHg in patients with proteinuria over 1.0 g/24 h and/or increased serum creatinine. To reach this BP targets three to four antihypertensive agents are usually necessary.

Guidelines for patients with DKD require a BP <130/80 mmHg [11,20,21]. The data supporting this guideline is based on analyses of clinical trials like HOT [18,22] and UKPDS 38 [6]. The ADVANCE study proves that the lowest risk for renal events was observed among subjects who achieved BP levels <110/65 mmHg [23].

3.3. Renin-angiotensin-aldosterone system blockade

The RAAS is an important target for hemodynamic disturbances in DKD. The pharmacological agents which block the RAAS slow the progression of renal dysfunction more effectively than other classes of antihypertensive agents. Currently available therapies for this blockade are ACEI, ARB and direct renin inhibitor [24].

ACEI or ARB

The first line therapy for hypertension in patients with CKD, is treatment with ACEI and/or ARB [3]. Nearly 80% of some US diabetic patients are receiving these agents.

RAAS blockade with ACEI or ARB confers an additional benefit on renal function. This renoprotective effect is independent of BP reduction [19,24]. These agents improve GFR, reduce the urinary albumin/creatinine ratio (UAER) and delay progression from microalbuminuria to macroalbuminuria. The antihypertensive effects combined with the nephroprotective effects of these agents support the recommendations of treatment guidelines that these drugs should be used in patients with DM and hypertension [20,21].

There are evidence suggesting that antihypertensive agents that modulate RAAS can delay the onset or even induce regression of microalbuminuria, lower the risk for appearance of clinical nephropathy and decrease mortality in patients with DM [25,26,27,28].

The role of ACEI in the prevention of diabetic **nephropathy** in patients with type 1 DM has not been very well documented. The use of perindopril during 3 years in normotensive normoalbuminuric type 1

diabetic patients delayed the increase in albuminuria [29].

In patients with type 2 DM, ACEI and ARB diminish the risk for diabetic **nephropathy** [30] and reduce the incidence of cardiovascular events [31]. In the MICRO-HOPE study [31], ramipril decreased the risk of overt **nephropathy** by 24% and the risk of cardiovascular death in patients with type 2 DM. In the BENEDICT trial, 1204 diabetic patients with hypertension, and normal UAE, were randomized to the non-dihydropyridine calcium channel blocker verapamil, the ACEI trandolapril, the combination of verapamil and trandolapril, or placebo. After a median follow-up of 3.6 years, the progression to microalbuminuria was signifcantly lower in the subjects treated with trandolapril or the combination (trandolapril and verapamil) compared with the subjects receiving only verapamil or placebo [8,27].

The ROADMAP study had as objective measurement of the impact of olmesartan treatment on renal outcome in 4400 patients with type 2 DM without microalbuminuria. Its results are expected for 2012 [32].

ACEI and ARB decrease UAE and the rate of progression from microalbuminuria to more advanced stages of diabetic **nephropathy**. A meta-analysis of 12 trials evaluating 698 nonhypertensive microalbuminuric type 1 diabetic patients showed that treatment with ACEI decreased the risk of progression to macroalbuminuria by 60% and increased the chances of regression to normoalbuminuria [33]. In a substudy of the PREVEND IT trial, fosinopril reduced UAE by 26% during the mean follow-up of 46 months [25].

ARB were also effective in reducing the development of macroalbuminuria in microalbuminuric type 2 diabetic patients. Irbesartan reduced the risk of progression to overt diabetic **nephropathy** by 70% in a 2-year follow-up study of 590 hypertensive microalbuminuric type 2 diabetic patients [34]. Additionally, a 38% reduction in UAE was observed, with 34% of patients reversing to normoalbuminuria. UAE was still reduced 1 month after the withdrawal of irbesartan [35].

In another study, valsartan produced a greater reduction in UAE than amlodipine (44 vs. 8%) with the same degree of BP reduction. These data plead for the idea that the antiproteinuric effect of ARB is BP independent.

The effect of replacement of an ARB with olmesartan (also an ARB) on early diabetic nephropathy in hypertensive patients with type 2 DM, was a significantly decrease of UAE. These results suggest the possibility that olmesartan may have more effect on early nephropathy than other ARB [36].

The use of either ACEI or ARB is recommended as a *first-line therapy* for type 1 and type 2 diabetic patients with microalbuminuria, even if they are normotensive [11].

In patients with type 1 DM and macroalbuminuria, ACEI therapy was shown to reduce albuminuria and also slow the rate of loss of GFR in the Collaborative Study Group captopril trial. Addition of ACEI in proteinuric type 1 diabetic patients [37] or ARB in macroalbuminuric type 2 diabetic patients [9,10] decreased proteinuria and renal function decline. In the ORIENT study, olmesartan has renal protective benefits in type 2 diabetic patients with overt proteinuria and renal insufficiency [37].

The beneficial effects of the RAAS blockers are dose dependent [24]. In the IRMA 2 study higher dose of irbesartan (300 mg vs 150 mg/day) was associated with less progression of microalbuminuria and improved kidney protection at the same BP response [34]. The use of candesartan at the dose of 128 mg/day (a dosage higher than the dosage recommended for the treatment of hypertension and heart failure) results in a significant reduction in UAE [13,38].

The initiation of treatment with ACEI in diabetic patients with serum creatinine levels over 1.4 mg/dl require careful monitoring of the renal function because serum creatinine might increase during the first 2 months, after that becoming stable. This raise in creatinine is associated with long-term preservation of renal function, and therefore ACEI should not be stopped. Greater increases should raise the suspicion of renal-artery stenosis. Inhibition of the RAAS, especially with ACEI, might raise serum potassium levels, particularly in patients with renal insufficiency. For these reasons, albuminuria, serum creatinine and potassium should be checked monthly during the first 2–3 months after starting treatment with ACEI or ARB.

If ACEI are not tolerated (mostly cough), ARB are an alternative. ARB are also the preferred agents for type 2 diabetic patients with left ventricular hypertrophy and/or micro- or macroalbuminuria [9,31,34].

Dual blockade of the RAAS with ACEI and ARB

The concept of dual blockade of the RAAS has been developed by Mogensen [38]. ACEI and ARB interrupt the RAAS at different levels and the combination of these classes of drugs may have an additive effect on renoprotection. Treatment with both ACEI and ARB in combination, may offer synergistic and complete blockade of the RAAS [39].

In a short-term trial, the dual blockade of the RAAS in patients with type 1 DM and DKD resulted in a drop in BP of 8/5 mmHg (24-hour ambulatory) and an additional significant (37%) drop in albuminuria in comparison with that of ACEI used alone [39].

In the CALM study [38], there was a reduction in BP of 10/6 mmHg and a tendency towards a more pronounced drop in UAE by 12 weeks with dual blockade (16 mg of Candesartan and 20 mg of Lisinopril) in comparison to either agent used alone [38].

This beneficial effect of dual blockade are not sustained by other studies. Parvanova *et al.* [40], in their study at the Steno Diabetes Centre, did not find additional antihypertensive and antialbuminuric effects of dual blockade relative to treatment with ACEI alone. In the IMPROVE study [41] dual RAAS blockade with ramipril and irbesartan did not reduce microalbuminuria to a greater extent than treatment with ramipril alone [41].

In the ONTARGET study [28], the combination of telmisartan and ramipril did not reduce the primary composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure compared with monotherapy. The combination therapy group had a significantly increased risk of renal dysfunction compared with the ramipril group. The percentage of patients with an increase in potassium level was similar in the ramipril and in the telmisartan group, but significantly higher in the combination-therapy group. The findings of the ONTARGET report would suggest the combination ACEI and ARB, become the exception rather than the rule, despite its enhanced antiproteinuric effects [28].

Dual blockade of the RAAS with ARB and direct renin inhibitor

The renoprotective effects of dual blockade of the RAAS with ARB and direct renin inhibitor (aliskiren) may be effective.

In the AVOID trial [42] was investigated the renoprotective effects of dual blockade of the RAAS by randomizing 599 patients who had type 2 DM with nephropathy and hypertension and were on the maximum recommended renoprotective dose of losartan, to the addition of either aliskiren or placebo. The addition of daily aliskiren was associated with a 20% reduction in the mean urinary ACR [42]. The benefits of aliskiren seemed to be independent of systemic BP.

The combination of aliskiren and valsartan, at maximum recommended doses, has been shown to provide significantly greater reductions in BP than monotherapy with either agent in patients with hypertension [43].

3.4. Combination therapy

If the treatment with ACEI and/or ARB does not allow reaching the BP target levels, then they can be combined with other drug classes, even before maximizing the dose of each agent. The combination of agents may include calcium channel blockers (especially nondihydropyridine), β-blockers, diuretics or central α_2-agonist.

Calcium channel blockers have an additional effect on reducing BP levels. These agents can be used in combination with an ACEI and/or diuretic and should be careful used in patients with a recent coronary event.

β Blockers are especially useful in patients with myocardial ischemia, since these drugs reduce cardiovascular events and mortality in patients with baseline pulse rate >84 bpm. Possibly, a metabolic neutral compound, carvedilol or nebivolol, should be used.

The combination of ß-blockers and nondihydropyridine calcium channel blockers should be used with caution, since both agents have negative inotropic, dromotropic and chronotropic effects.

An ACEI or ARB and a low-dose thiazide diuretic (12.5–25 mg/day) can be initially used, but loop diuretics (furosemide) should be used in the place of thiazides in patients with GFR <30 ml/min, corresponding to a serum creatinine of 2.5–3.0 mg/dl.

The ADVANCE trial demonstrated that routine administration of a fixed combination of the ACEI perindopril and the diuretic indapamide significantly reduced combined microvascular and macrovascular outcomes, the CVD and total mortality [23].

Small studies have reported that use of spironolactone, an aldosterone receptor antagonist, may be associated with a reduction of proteinuria and slower progression of kidney disease [44]. The use of an aldosterone antagonist, especially in combination with an ACEI or ARB, increases the possible development of hyperkalemia.

Some authors [45] support the continued use of ACEI or ARB in patients with more advanced CKD, in combination with diuretics, calcium channel blockers, β-blockers, diuretics and vasodilators, only with very close monitoring of eGFR, serum creatinine and serum potassium.

Antihypertensive substitution with calcium channel blockers (amlodipine, lercanidipine), selective α_2-adrenergic and imidazoline receptor agonist (moxonidine, rilmenidine), hydralazine and/or methyldopa, in place of ACEI and/or ARB, in selected

patients presenting with accelerated renal-failure, ensured achieved BP goals while still allowing for often improved and stable improved kidney function, even years later [45].

4. Conclusion

In patient with DKD the BP target level is lower than 130/80 mmHg.

The measures shown to prevent the onset or attenuate the progression of DKD include: glycemic and BP control, specific interruption of the RAAS, with either ACEI or ARB and potentially lipid-lowering therapy.

Management of hypertension in patients with DKD is complex because both, DM and CKD, alters the pharmacokinetic and pharmacodynamic of many drugs, thus a great care must be taken, not only in adjusting the dose of antihypertensive medications, but also in considering their potential to ameliorate or exacerbate CKD progression.

The antihypertensive agents who modulate RAAS are the first line therapy. They can delay the onset or even induce regression of microalbuminuria, retard progression from microalbuminuria to macroalbuminuria, reduce the urinary ACR and improve GFR. However could be the instigating factor for worsening renal failure in (older) CKD patients, and many need to be discontinued in selected patients.

The greatest challenge in managing hypertension in CKD patients with DM is achieving the lower level of BP recommended.

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