MANAGEMENT OF ARTERIAL HYPERTENSION IN ADULTS WITH DIABETES AND CHRONIC KIDNEY DISEASE

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1. INTRODUCTION

Diabetes and hypertension, along with dyslipidemia and smoking, acting separately or combined, are the main risk factors of atherosclerotic cardiovascular disease that is responsible for the death of most adults.

The aggravating role of hypertension associated with diabetes is supported by numerous studies, especially by the results of United Kingdom Prospective Diabetes Study (UKPDS), which showed that BP reduction has a favorable impact on the evolution and complications of diabetes, equivalent to that of an optimal glycemic control.

These are only two arguments that support the need for serious addressing, assessing and treatment of the two pathological conditions (diabetes and hypertension) whose association concerns approximately 50% of the patients with type 2 diabetes.

Hypertension is the most important co-existing risk factor for death at a young age of patients with type 2 diabetes. Almost 75% of cardiovascular complications in patients with diabetes can also be attributed to hypertension. The presence of diabetes in a hypertensive patient involves his inclusion in a high-risk or very-high-risk group independently of BP values, the target organ damage and the presence of other risk factors or other cardiovascular diseases [2].

UKPDS showed that the presence of hypertension is a risk factor for microalbuminuria and retinopathy and that reducing the incidence of chronic complications was significantly associated with the amplitude of systolic BP (Blood Pressure) decrease, the lowest risk corresponds to a systolic BP below 120 mmHg [3].

Reduction of elevated BP in patients with diabetes and hypertension is mandatory, as it turned out that this decrease is beneficial for reducing the frequency of diabetes-related complications, cardiovascular events and mortality [3].

Management of hypertension is essential for minimizing the decline rate of eGFR (Glomerular Filtration Rate) because virtually all patients with CKD (Chronic Kidney Disease) have hypertension and prospective studies have shown that the association hyperglycemia-hypertension is the most unfavorable risk constellation for the development of ESRD (End Stage Renal Disease), as well as for the cardiovascular morbidity/mortality. The therapeutic target for BP in patients with diabetes and DKD (Diabetic Kidney Disease) is 130/80 mmHg (lower than in the general population) [3].

CKD can be found in up to 23-25% of patients with Diabetes Mellitus (DM)[4]. DM is the primary cause of kidney failure, and the diabetic patients represent 45% of those who receive dialysis therapy.

2. DIABETIC KIDNEY DISEASE: SCREENING AND CLINICAL DIAGNOSIS

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 [5].

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.

Blood pressure (BP) level is a major determinant of cardiovascular morbidity and mortality in individuals with diabetes mellitus. Hypertension and diabetes mellitus 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 is 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: hypertension, diabetes mellitus, diabetic kidney disease.
in a 24-hour urine collection, or > 200μg/min in a timed urine collection [5]-Table 1.

Table 1—Definitions of abnormalities in albumin excretion

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot collection (mg/g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–299</td>
</tr>
<tr>
<td>Macro (clinical)-albuminuria</td>
<td>≥300</td>
</tr>
</tbody>
</table>

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.

Perform an annual test to assess urine albumin excretion in type 1 diabetic patients with diabetes duration of 5 years and in all type 2 diabetic patients starting at diagnosis. Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present [3] - Table 2.

Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD). Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes. Microalbuminuria is also a well-established marker of increased CVD risk [31,32]. Patients with microalbuminuria who progress to macroalbuminuria (≥300 mg/24 h) are likely to progress to ESRD [33,34]. However, a number of interventions have been demonstrated to reduce the risk and slow the progression of renal disease.

The interventions which proved to prevent the onset or attenuate the progression of DKD are: glycemic and blood pressure (BP) control [1,6], specific blockade of the renin-angiotensin-aldosterone 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 [9].

Hypertension is commonly found in patients with DKD, its prevalence is estimated to be from 30 to 90%, with higher prevalence in patients with albuminuria [2]. Uncontrolled hypertension determine a higher risk of cardiovascular events, including death, increasing proteinuria and progression of kidney disease [10].

The goals of antihypertensive therapy in patients with CKD are to lower BP, reduce CVD risk and slow the progression of CKD [9,11,12].

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 [13]. The presence of microalbuminuria or microproteinuria requires more aggressive treatment to achieve the recommend 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 [14].

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 [15,16].

In normoalbuminuric diabetic patients, the treatment of hypertension reduces the risk of cardiovascular and microvascular events [12]. In 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 [16].

### Table 2. Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min per 1.73 m² body surface area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage* with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage* with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 sau dializa</td>
</tr>
</tbody>
</table>

*Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging tests.
In the UKPDS, the reduction of systolic BP, from 154 to 144 mmHg, reduced the risk for the development of microalbuminuria by 29% [1].

Microalbuminuria is an indicator of endothelial dysfunction and an independent marker for cardiovascular morbidity and mortality in individuals with and without DM [12]. 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 [14]. 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 [16].

Guidelines for patients with DKD require a BP< 130/80 mmHg [3,20,21]. The data supporting this guidelines is based on analyses of clinical trials like HOT[18,22] and UKPDS [1]. The ADVANCE study proves that the lowest risk for renal events was observed among subjects who achieved BP levels <110/65 [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 [24].

The first line therapy for hypertension in patients with CKD, is treatment with ACEI and/or ARB [16]. 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 effects 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 [16,25,27].

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 [26].

In patients with type 2 DM, ACEI and ARB diminish the risk for diabetic nephropathy and reduce the incidence of cardiovascular events [27]. In the MICRO-HOPE study [28], ramipril decreased the risk of overt nephropathy by 24% and the risk cardiovascular death in patients with type 2 DM.

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 [3].

The beneficial effect 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 [29]. 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 inUAE [12,30].

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 nondihydropiridine), β-blockers, diuretics or central α2-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 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 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 (coronary vascular disease) and total mortality [23].
4. TREATMENT STRATEGIES FOR DIABETIC KIDNEY DISEASE

In the treatment of the non pregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used. While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements: In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.

In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria.

In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been shown to delay the progression of nephropathy. If one class is not tolerated, the other should be substituted. Reduction of protein intake to 0.8 –1.0 g/kg body weight/day in individuals with diabetes and the earlier stages of CKD and to 0.8 g/kg body weight/day in the later stages of CKD may improve measures of renal function (urine albumin excretion rate, GFR) and is recommended.

When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of acute kidney disease and hyperkalemia. Continued monitoring of urine albumin excretion to assess both response to therapy and progression of disease is recommended. When eGFR <60 ml/min/1.73m², evaluate and manage potential complications of CKD. Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR), difficult management issues, or advanced kidney disease.

Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset of microalbuminuria and the progression of micro- to macroalbuminuria in patients with type 1 [35,36] and type 2 diabetes. The UKPDS provided strong evidence that control of blood pressure can reduce the development of nephropathy. In addition, large prospective randomized studies in patients with type 1 diabetes have demonstrated that achievement of lower levels of systolic blood pressure (<140 mmHg) resulting from treatment using ACE inhibitors provides a selective benefit over other antihypertensive drug classes in delaying the progression from micro- to macroalbuminuria and can slow the decline in GFR in patients with macroalbuminuria [1,37]. In type 2 diabetes with hypertension and normoalbuminuria, RAS (Renin Angiotensin System) inhibition has been demonstrated to delay onset of microalbuminuria.

In addition, ACE inhibitors have been shown to reduce major CVD outcomes (i.e., myocardial infarction, stroke, death) in patients with diabetes, thus further supporting the use of these agents in patients with microalbuminuria, a CVD risk factor. ARBs do not prevent microalbuminuria in normotensive patients with type 1 or type 2 diabetes [38,39]; however, ARBs have been shown to reduce the rate of progression from micro to macroalbuminuria as well as ESRD in patients with type 2 diabetes [40,41]. Some evidence suggests that ARBs have a smaller magnitude of rise in potassium compared with ACE inhibitors in people with nephropathy [3]. Combinations of drugs that block the rennin angiotensin-aldosterone system (e.g., an ACE inhibitor plus an ARB, a mineral corticoid antagonist, or a direct renin inhibitor) have been shown to provide additional lowering of albuminuria [30,9]. However, the long-term effects of such combinations on renal or cardiovascular outcomes have not yet been evaluated in clinical trials, and they are associated with increased risk for hyperkalemia.

Other drugs, such as diuretics, calcium channel blockers, and β-blockers should be used as additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs [3], or as alternate therapy in the rare individual unable to tolerate ACE inhibitors or ARBs. Studies in patients with varying stages of nephropathy have shown that protein restriction of dietary protein helps slow the progression of albuminuria, GFR decline, and occurrence of ESRD [42,43]. Dietary protein restriction should be considered particularly in patients whose nephropathy seems to be progressing despite optimal glucose and blood pressure control and use of ACE inhibitor and/or ARBs [43].

5. 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.
The greatest challenge in managing hypertension in CKD patients with DM is achieving the lower level of BP recommended.

References