RENIN - ANGIOTENSIN SYSTEM EFFECTS ON DIABETIC PATIENTS WITH MICROALBUMINURIA

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Abstract

The diabetic nephropathy, multifactorial disorder that results from interaction between both environmental and genetic factors, is the most common cause of end stage renal failure in the developed countries.

Microalbuminuria, the first sign of renal injury, have been demonstrated to be a strong, independent marker for renal involvement, as well as for cardiovascular disease and overall mortality in both type 1 and type 2 diabetes.

The new information strongly correlates development of microalbuminuria with the renin-angiotensin system, a major regulatory system of cardiovascular and renal function.

Both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are recognized as first-line antihypertensive therapy at diabetic patients with nephropathy. The benefits of these drugs on reducing the progression of nephropathy exceed their antihypertensive effects, that claim other mechanisms to be also involved.

Key words: diabetic nephropathy, microalbuminuria, renin-angiotensin system

Introduction

The diabetic nephropathy is the most common cause of end stage renal failure in the developed countries and as the diabetes mellitus is increasing in prevalence worlwide, the financial costs necessary for dialysis and transplantation are also increasing.[1,2] The diabetic patients with nephropathy have a greater rate of cardiovascular morbidity and mortality when compared with those without diabetic nephropathy.[3] All of these are reasons for which the diabetic nephropathy is an important health matter.

As a result of the improved treatment of cardiovascular complications, it has been observed the incrising of the incidence of diabetic nephropathy in patients with type 2 diabetes[4] in the last years, and now the percentage of patients who have nephropathy is almost the same for type 2 and type 1 diabetes. Diabetic nephropathy occurs in 30% to 50% of patients type 1 or type 2 diabetes.[5,6]

The first sign for renal involvement in diabetic patients is in general micro-albuminuria (the presence in urine of 30 to 299 mg of albumin per 24 hours or of 20 to 199 μg per minute in an overnight urine sample) and this stage is classified as „incipient nephropathy".[7,8] When albumin levels exceed 300 mg per 24 hours, this condition is called proteinuria or overt nephropathy. Proteinuria has been studied as a marker of dynamic renal injury; in this direction, several clinical trials have shown that impaired renal function in patients with high-grade proteinuria (more than 1 gram per 24 hours) progresses at a faster rate than those

with low-grade proteinuria (less than 1 gram per 24 hours).[9] Moreover, once macroalbuminuria is present, creatinine clearance declines at a rate of 10 to 12 ml per minute per year in untreated patients.[4,10] We cannot say the same thing about the diabetic patients who have only microalbuminuria, because only 20 to 40 % of pacients with microalbuminuria will progress to overt proteinuria.[11,12] Even so, all the patients with microalbuminuria need to be treated as if they are going to progress to more severe renal disease.

Microalbuminuria is not only a marker for renal involvement, but also an independent marker of increased cardiovascular morbidity and mortality in both type 1 and type 2 diabetes.[13] This aspect is very important regardind the fact that cardiovascular diseases represent un important pathology associated to diabetes, beeing responsable for 75% of hospital admissions and death in diabetic patients.[14]

Microalbuminuria of short duration (regardless of the duration of diabetes) is more likely to regress than microalbuminuria of long duration and it has also been suggested that short-term improvement in albuminuria may have a favourable impact on long-term renal prognosis.[15] Early recognition of renal disease increases the chance to prevent the progression of diabetic nephropathy, that is why screening for microalbuminuria is important at the diabetic patient as a preventing strategy.[16] Microalbuminuria can be confirmed and quantified by measuring the rate of albumin excretion in a 24 hours or overnight urine sample. Another method that allow both diagnosis and follow-up of microalbuminuria is by measuring the ratio of albumin to creatinine in a morning urine sample (normally less than 30 μg of albumin per milligram of creatinine).[17]

In general, in type 1 diabetes the incidence of diabethic nephropathy increases about 5 years after diagnosis, with the highest incidence at 5 to 15 years after diagnosis. In type 2 diabetes this data is not so clear because of the indefinite start of the disease. The screening for microalbuminuria, that can allow early therapeutic intervention, should be done for patients with type 1 diabetes at 3 to 5 years after diagnosis, and for patients with type 2 at the moment of the diagnosis.

The new information that strongly correlates microalbuminuria with metabolic syndrome proved that the therapy that inhibit the renin-angiotensin system is the best choice for decreasing both proteinuria and blood pressure at diabetic patients.[18,19]

Elements of Pathogenesis

Chronic hyperglycaemia is the first cause of diabetic nephropathy in both type 1 and type 2 diabetes. In type 1 diabetes, the hyperglycemia is frequently the only cause identified for renal injury; and so, the natural progression of renal disease in type 1 diabetes is well characterized. On the contrary, in type 2 diabetes the renal involvement is a heterogeneous mixture of different factors. In type 2 diabetes, hyperglycaemia starts after the fourth decade of life, when the kidneys have already progressive glomerulosclerosis caused by ageing. Also, in type 2 diabetes there can be present other causes that determine chronic renal disease, like arterial hypertension, obesity, dyslipidaemia, and smoking.[20] In general, pure diabetic

glomerulopathy can be observed in the stage of microalbuminuria (incipient nephropathy).[21] Progression of renal disease is more uniformly in type 1 diabetes than in type 2 diabetes, where the course of the renal disease is difficult to establish.

Hiperglycaemia is the pathogenic factor for which it was well-established the implication for the onset [3,22,23,24,25] and progression[3,22,26,27,28] of microalbuminuria. The tight glucose control is so very important in the management of diabetic nephropathy and the recommendation in both type 1 and type 2 diabetes is to aim for HbA_{1c} values of less than 7%.

Hypertension is an early abnormality that can precede or predict the presence of renal injury in patients with type 1 diabetes and a common association in patients with type 2 diabetes. Hypertension is an important risk factor for the progression of renal disease in both type 1 and type 2 diabetes [29,30], even more important for renal protection than lowering glucose levels.[31]

American Diabetes Association (ADA) and The Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) recommended 130/80mmHg in diabetic microalbuminuric patients[5,32,33] and then a target as low as 125/75 mmHg has been proposed with proteinuria of greater than 1 g per 24 hours. [34,35] For optimal renal protection, the clinical study confirms that the main arterial pressure should be at least 92 mm Hg (corresponding to a blood pressure of about 130/70 mm Hg).[36] In order to achive these targets almost all of the patients require polypharmacy.[37,38,39] JNC-VII recommends initiation of therapy with two drugs when blood pressure is 20/10 mm Hg above goal.[32] The blood pressure control should not be overstated because it was observed that if diastolic pressure was less than 70mmHg the rates of cardiovascular events are increasing.[40]

Dyslipidaemia is characteristically associated with type 2 diabetes. More than the well known role of dyslipidaemia in cardiovascular pathology and also in renal ischemic disease, it was demonstrated that hypercholesterolaemia induces un upregulation of vascular AT1 receptor expression leadind to enhanced release of free radicals and increased vasoconstriction and cell proliferation. Statins decreased proteinuria and preserved the glomerular filtration rate in patients with renal impairment not entirely by a reduction in blood cholesterol, but also by a direct effect of downregulate AT1 receptors expression.[41,42]

Smoking is another independent risk factor described for the onset and development of nephropathy; the microalbuminuria is more important in cigarette smokers[25] and also smoking cessation alone seems to reduce the risk of renal disease progression by 30 %.[43]

The diet is certainly very important in the diabetic nephropathy management by improving glycemic control. Moreover dietary changes can improve blood pressure regulation by reducing sodium intake. Also, in diabetic nephropathy is recommended a low-protein diet, less than 0.8 g/kg daily but not less than 0,6 g of protein per kilogram daily in order to avoid malnutrition. The lowering protein intake leads to low glomerular filtration rate and a low glomerular hydrostatic pressure and trials have demonstrated that a

low-protein diet can reduce the progression of diabetic nephropathy.[44,45,46]

The Renin-Angiotensin System (RAS)

The renin-angiotensin system is a major regulatory system of cardiovascular and renal function, which cascade begins with the production of angiotensinogen in the liver. Under the influence of sympathetic stimulation of β_1-adrenoceptors, renal artery hypotension or decreased sodium in the distal renal tubules, renin is released by the kidney. Renin hydrolyzes angiotensinogen to angiotensin I, a relatively inactive precursor. Angiotensin I is cleaved by angiotensin converting enzyme (ACE) to the active angiotensin II. Two major classes of angiotensinogen receptors were discovered, AT1 and AT2. AT1 receptors have been better described and the known physiologic effect of angiotensin II is determined by selective binding to these receptors. AT1 receptors are present in different tissues, including kidney, heart, brain, systemic vasculature, adrenal gland, and liver.[47]

Circulating angiotensin II is formed in the blood by the classic RAS. Angiotensinases rapidly destroy angiotensin II (half-live aprox 1min), while the half-live of renin is more prolonged (10 to 20min). In addition to classic RAS, many tissues have the ability to locally produce angiotensin II; these tissues include the uterus, placenta, vasculat tissue, heart, brain, and, particularly, the adrenal cortex and kidney.[48]

Recent studies demonstrate that intrarenal angiotensin II production is important in patients with renal disease[49], but the relative contribution of systemic versus intrarenal angiotensin II production is difficult to establish. It was estimated that 40% of the angiotensin that acts locally in the kidney is produced in intrarenal independent pathways.[50]

In the kidneys, angiotensin II constricts glomerular arterioles, having a greater effect on efferent arterioles than afferent and so increasing glomerular pressure. Independent of its systemic hemodynamic activity, angiotensin II have a various of effects by binding the angiotensin II receptors located on different renal tissue cells.[51] In diabetic patients, hyperglicaemia induces hiper-production of angiotensin II by mesangial cells and also upregulation of angiotensin II receptors.[52]

Angiotensin II has growth factor properties by activating transforming growth factor β, and via transforming growth factor β inducing matrix deposition in both mesangial and tubular cells[53] and apoptosis in glomerular epithelial cells[54], being involved in the podocyte abnormalities.[55] All these phenomenons determined by angiotensin II are exacerbated at diabetic patients and contribute to the progression of renal disease.[56]

Angiotensin II inhibits the diferentiation of adypocytes through the AT1 receptors determining low adiponectin levels and also inhibits the peroxisome proliferator-activated receptors γ (PPARγ) that are associated with insulin resistance.[57,58]

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

Angiotensin-converting enzyme inhibitors (ACEIs) block the conversion of angiotensin I to angiotensin II, initially leading to a dramatic fall in plasma and also in tissues of angiotensin II levels.[58] With continued treatment, angiotensin II seric concentrations gradual return to pretreatment values, the phenomenon of „ACE escape".[59] ACEIs block only the classic pathway of angiotensin II formation, so this „ACEI escape" phenomenon is explained by activating the alternative pathways that generate angiotensin II. Enzymes in human tissues like chymase, cathepsin G, and chymostatin-sensitive angiotensin generating enzyme can form angiotensin II from angiotensinogen and possible from other peptide substrates[47,60] and increased ACE activity in atheromatous lesions in vessel walls.[61] The sustained antihypertensive action of ACEIs, after the recurrence angiotensin II seric levels, is due to their ability of blocking the metabolism of bradikinin, a potent endothelium-dependent vasodilatator and to the effect of inhibiting sympathetic nervous system.[62,63]

ACEIs is the first-line antihypertensive therapy to choose for the diabetic patients with nephropathy.[64,65] Thiazide diuretics and beta-blockers are not the first option in diabetic patients given the fact that these drugs can promote glucose intolerance.[66,67,68,69,70] ACEIs are better tolerated on diabetic patients and may also improve insulin sensitivity and decrease the risk of glucose intolerance.[71,72] At the begining it was unclear whether this findings might be attributable to adverse metabolic effect of the non-ACEIs drugs taken in analysis. These benefic effects on glicemic metabolism have been proven to be a characteristic of ACEIs and are due to improved blood flow through the microcirculation of skeletal-muscle tissue and to amended insulin action in mediating glucose transport at the cellular level.[73,74]

Calcium-channel antagonists have not been found to have any metabolic effect, but, for lowering the blood pressure and the levels of urinary albumin, ACEIs and ARBs appear to be the most effective agents.[75,76]

ACEIs are effective in reducing the risk of the onset or progression of overt nephropathy, and renal benefits are greater than those attributable to the decrease in blood pressure.[40,77] The renoprotective effect of ACEIs was first demonstrated on patients with nephropathy due to type 1 diabetes[78], other trials have demonstrated the renal benefits of ACEIs for renal involvement in type 2 diabetes.[79,80,81] This renoprotection was also demonstrated in nondiabetic nephropathy.[82,83] The renal protective effect appears to be present for all agents in the ACE inhibitor class and the difference betwen ACEIs in the reduction of proteinuria appear not to be significant.[84]

Angiotensin receptor blockers (ARBs) block the specific interaction of angiotensin II on the AT1 receptors, inhibiting in this way the angiotensin II effects: vasoconstriction, salt and water retention, stimulation of sympatetic activity or cellular proliferation.[85,86,87,88] By acting directly at the AT1 receptor's site responsable for all known clinical actions of angiotensin II, ARBs appear to be more effective in blocking RAS, because the angiotensin II ACE-independent pathways are also affected.[89] The consequence of

chronic increased circulating concentration of angiotensin II have not been yet well established. Additional benefic effects of ARBs may be related to stimulation of the AT2 receptors by the free angiotensin II because the absence of AT2 receptors may produce accelerated fibrosis and collagen deposition in interstitium.[90] Other opinion is that AT2 receptors may be involved in some of the harmful effects of angiotensin II.[91]

ARBs were introduced in clinical practice as an alternative to ACEIs for managing diabetic nephropathy.[92] ARBs have no influence on bradykinin metabolism, and so, they can be used for those patients that accuse adverse reaction like cough at ACEIs administration.[93,94,95] In the presence of renal insufficiency, ARBs administration raised the serum potassium less than ACEIs.[96]

Clinical trials have demonstrated the efficacy of ARBs in reducing blood pressure[97], with a potency equal to that of other antihypertensive drugs.[98] The use of ARBs also provides renoprotection that exceeds the one attributable to blood pressure lowering alone.[99] ARBs are now consider, as ACEIs, first-line antihypertensive therapy for type 2 diabetic patients. The trials results strongly support the use of ARBs in patients with type 2 diabetes nephropathy.[100,101]

Both ARBs and ACEIs are recognized as first-line antihypertensive therapy at diabetic patients with nephropathy. The benefits of these drugs on reducing the progression of nephropathy exceed their antihypertensive effects that prove other mechanisms to be also involved.[99,102,103]

Proteinuria is a strong and independent marker for renal disease progression.[104] The presence of proteinuria determine a vicious cycle, excessive protein overload induce tubulointerstitial damage[105], excessive accumulation of proteins in tubular epithelial cells induce the locally secretion of vasoactive and inflammatory cytokines that injure in addition the tubulointerstitium determined the progression of renal disease.[104,106,107]

The mechanism of renoprotection by agents that block the action of angiotensin II is complex, involving not only hemodynamic factors that lower intraglomerular pressure, but also decrease transforming growth factor β production[108,109,110] therefore decrease collagen formation[111], conffering long-term renal protection.[112]

Angiotensin II increases glomerular permeability to protein and impairs the size-selective function of the glomerular filtre.[113,114] Agents that block the action of angiotensin II reduce the proteins filtration across the glomerular capillary wall[115] and the glomerular membrane permeability.[116]

Also, agents that block the action of angiotensin II reduce the expression of nephrin, protein implicated in the pathogenesis of proteinuria in diabetic patients.[117,118]

Even the clear benefits for ACEIs in diabetic nephropathy were demonstrated in type 1 diabetes, as for ARBs in type 2 diabetes, other trials indicate the utility of ACEIs in type 2 diabetes[119] and also the similar reductions in proteinuria and systemic blood pressure for ARBs and ACEIs in patients with type 1 diabetes.[121,122]

Recent evidence suggests that the use of an ACEIs and an ARBs in combination offers a further benefit in reducing proteinuria. These two drugs affect the RAS at different levels and thus may have an additive

antuhypertensive and antiproteuric effect when used in diabetic pacients.[122]

Using only one class of agents that block the action of angiotensin II may not be completely effective for RAS blockade.[60,123,124] The CALM study showed that combination treatment was significantly more effective in reducing proteinuria and diastolic pressure in type 2 diabetes than either agent alone.[125] Same results, that sustained the synergic effect of this two class of drugs, were found in other trials in type 2 diabetes[126,127] and also in type 1 diabetes[128,129], effect that is preserved even on a long period of administration.[128,130]

Concerns that have been raised regarding the combination therapy are the risks for hiperkaliemia and acute worsening of renal function. In this direction, it is important to emphasize the combination therapy with ACEIs and ARBs did not have significant increase the serum potassium in patients without renal insufficiency.[122,126,128,130]

Therefore, the dual blockade may be used in patients with diabetic nephropathy that have been responding poorly to previous antihypertensive treatment, including administration of either ARBs or ACEIs in monotherapy. The administration of the combination therapy should be closely followed, in order to prevent possible side effects like hyperkaliemia and acute worsening of renal function.

New Therapies for Renin - Angiotensin System

Eplerenone is newer aldosterone blocker, which contrary to spironolactone is a selective aldosterone blocker. Eplerenone seems to be efficient in reducing blood pressure when added to ACEIs or ABRs therapy[131] and also to have an additive antiprotenuric effect when added to ACEIs.[132]

Aliskiren is a recent approved oral renin inhibitor. By inhibiting renin itself, aliskiren would improve blood-pressure control and might modify other actions and interactions of this important vasoactive system. Also, the renin activity is reactive increased in patients with ACEIs or ARBs therapy for long periods. Aliskiren show efficacity in reducing blood pressure[133,134] and even microalbuminuria[135], but the research is still unfinished.

Conclusion

The blockade of renin-angiotensin-aldosteron system has been proved to be the central part of antihypertensive therapy in diabetic patients. Both agents that block the action of angiotensin II, ARBs and ACEIs, are recognized as first-line antihypertensive therapy at diabetic patients with nephropathy. The benefits of these drugs on reducing the progression of nephropathy exceed their antihypertensive effects and may be used in low dosage even in normotensive pacients with diabetic nephropathy as prevention therapy. Recent evidence suggests that the use of an ACEIs and an ARBs in combination offers a further benefit in reducing proteinuria, but some more information is needed for this approach. Some new therapies that interfere with renin-angiotensin system, eplerenone and aliskiren, have been recently introduced for clinical use.

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