Blood presure management in diabetic patients

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Introduction

Diabetes is a major risk factor for cardiovascular morbidity and mortality. It has long been known the increased prevalence of hypertension in diabetic patients, that is approximately 2 times greater than in matched non-diabetic population [1,2]. The coexistence of hypertension in the diabetic subject act as an additive risk factor for vascular complications. While hypertension in insulin-dependent diabetes mellitus (IDDM) is almost exclusively attributed to the diabetic renal disease, in non-insulin-dependent diabetes (NIDDM) is frequently related to insulin resistance. Different physiopathogenic factors may determine different antihypertensive approaches in diabetes. There is an apparent consensus that hypertension should be aggressively treated in diabetic patients.

In 1987, the Working Group on Hypertension in Diabetes published the "final report" proposing a list of drugs as first-line therapy for hypertensive diabetic patients [3]. Further reports showed that the final chapter on this issue is still to be written[4,5]. We review part of the therapy currently recommended for hypertensive subjects with diabetes. Particular adverse effects on carbohydrate and lipid metabolism are focused, as well as on the chronic angio and neuropathic complications of diabetes.

Physiopathogenic considerations

Increased exchangeable sodium pool is observed in patients with IDDM[6-8] and the excess body sodium accompained by fluid retention may play an important role in elevation and maintenance of high blood pressure (BP) in diabetes-asociated hypertension. Several metabolic and hormonal abnormalities are involved in renal sodium retention, such as hyperglycemia, hyperinsulinemia and altered secretion or action of atrial natriuretic peptide. High body sodium may potentiate the pressor role of angiotensin II [9] Therefore, sodium excretion promoting drugs could be desirable when treating hypertension at least in a subset of diabetic subjects.

Besides common pressor mechanisms, IDDM and NIDDM have some particularities concerning their physiopathogenesis. In IDDM, BP elevation parallels the development of nephropathy and most studies have suggested that hypertension is a consequence of diabetic renal disease [10] Renal hemodynamic disturbances, such as intraglomerular hypertension and hyperfiltration, are implicated in the genesis of nephropathy in IDDM. Slightly abnormal loss of albumin in urine (microalbuminuria) could unmask the renal injury, that is commonly associated with increased blood pressure levels. Early intervention on this stage of incipient diabetic nephropathy, where aggressive antihypertensive treatment is included, has shown the best results in postponing its progression [11]. Whereas patients with IDDM usually remain normotensive before the development of proteinuria, a great proportion of NIDDM are already hypertensive when the disease is diagnosed [12], although the high prevalence of hypertension in this population also increases markedly as proteinuria develops[13]. Thus, in NIDDM hypertension seems to be related not only to the presence of diabetic nephropathy but mainly to other factors. such as insulin resistance and hyperinsulinemia. In fact, it has been described a multifaceted syndrome responsibls for both, NIDDM and hypertension, besides obesity, dyslipidemia and atherosclerotic cardiovascular disease[14].

Considering the pathogenic aspects of hypertension in diabetes, it is reasonable to suppose that ideal antihypertensive therapy in IDDM should also correct early renal hemodynamic disturbances, attempting to preserve renal function. On the other hand,

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hypertension in NIDDM may be seen as part of the large spectrum of insulin resistance syndrome, where the pharmacological reduction of BP is only a part of its treatment.

Antihypertensive treatment in diabetes

Although long-term trials demonstrated effectiveness of antihypertensive treatment in reducing death due to stroke and heart failure in nondiabetics, the decrease in coronary artery disease mortality was not shown yet[15]. In diabetic patients, a particular group at high risk for death from coronary artery disease, randomised studies concernins the benefits of antihypertensive therapy on its prevention, have not been conducted yet. On the other hand, convincent data focusing the microangiopathy in IDDM, have emphasized the importance of adequate BP control for the decline in the rate of deterioration in renal function [16]. Some investigators have even proposed certain levels of mean BP for maintaining or decreasing microalbuminuria and glomerular filtration rate in diabetic patients at risk for clinical nephropathy[17].

Once the diagnose of hypertension is established in the diabetic patient, initial non-pharmacological approach (weight loss, sodium restriction, lifestyle modifications, physical exercise) is recommended. Some of the pharmacological options in treating these patients will be focused herein. Recent studies have suggested a preferential use of angiotensin-converting enzyme (ACE) inhibitors and also calcium channel blockers (CCB) when treating hypertension in diabetic patients. However, diuretics and beta-blockers are the only classes of drugs shown thus far to reduce morbidity and mortality in a significant number of nondiabetic hypertensive subjects in long-term clinical trials.

a) Diuretics

Although diuretic therapy has been associated with the occurrence of glucose intolerance in several clinical trials for hypertension[18], these drugs are still considered a first-line therapy for hypertensive subjects with diabetes[19]. Their use is mainly based on the sodium excretion promoting effects, since diabetics have frequently an increased pool of sodium. Thiazides have been shown effective in treating hypertension in this population and, in microalbuminuric IDDM, the BP lowering effect is accompanied by decreased urinary albumin excretion and renal functional deterioration". In our series, the changes in albuminuria were correlated to BP reductions[21]. However, the adverse effects on carbohydrate and lipid metabolism have motivated some controversy in using in diabetic subjects. Indeed, increased mortality associated with diuretic therapy in a selected group of diabetic patients was recently reported [22]. Besides, speculation persists concerning the idea that diuretic-treated hypertensive diabetics could become harder to achieve euglycemic control. It is well established that potassium plays a central role in normal regulation of insulin secretion and that its repletion can correct such insulin secretion inhibition[23]. Decreased insulin secretion and enhanced insulin resistance have been considered mechanisms underlying the diuretic associated disturbances on glucose metabolism[24], although conflicting results were obtained concerning the latter mechanism[25,26]. A study conducted in our clinic[27] confirmed previous ones[28] showing deterioration in glucose homeostasis during chlorthalidone therapy and suggested that potassium depletion may to be involved in the increase in insulin resistance. Thus, in a subset of diabetic patients, diuretic therapy appears be related to changes in glycemic control. However, Moser and Ross experiences suggested that the long-term use of this medication will occasionally make control more difficult[5]. They also considered of debatable clinical significance the elevation in serum cholesterol that occurs early in thiazide therapy [29], in spite of blunting, to some extent, the beneficial effects of a low-fat diet. Until this moment, available data do not support the warning to exclude diuretics in the treatment of hypertensive diabetic patients.

b) *Beta-blockers*

A complex mechanism, involving cardiovascular and renal effects, mediates the BP reduction following the use of beta-adrenergic blocking agents. They may be contraindicated in a subset of diabetic patients that are particularly at risk for cardiovascular complications, such as congestive heart failure and peripheral arterial disease. On the other hand, a protective effect on the reoccurence of ischemic heart attack has been shown. Their potential adverse effects on glucose and lipid metabolism may also limit the use in diabetics. It is well documented the beta-adrenergic effects on insulin secretion and hepatic glucose output[30]. Blockade of beta receptors decreases insulin secretion and can potentially deteriorate glucose homeostasis in NIDDM [31], but the use of cardioselective blockers seems to minimize these effects [32]. Episodes of hypoglycemia can be more difficult to be recovered in beta-blockers treated diabetic patients. Hepatic mechanisms responsible for glucose release

in response to hypoglycemia are inhibited by these drugs. In addition, in IDDM beta-blockers compromise the counteregulation process following hypoglycemia[33], besides blunting the usual hypoglycemic symptoms. Unfavorable effects of beta-blocker therapy have been described, including increase in serum triglyceride and VLDL-cholesterol and decrease in HDL-cholesterol levels[34]. This aspect gains importance if the patient has dyslipidemia besides NIDDM, as features of the insulin resistance syndrome. Considering the effectiveness of these antihypertensive drugs, beta-blockers have still being indicated for the treatment of diabetic patients, keeping in mind the possibility of such adverse effects. Cardioselective agents should be preferred.

c) Angiotensin-converting enzyme inhibitors

This class of antihypertensive drugs has been the most studied in recent years. The main mechanism involved on the vasodepressor action of ACE inhibitors is related to the decrease in the pressor substance, angiotensin II, and also to the increase in bradikinin production, resulting in diminished peripheral vascular resistance. Several experimental and human studies have suggested the ACE inhibition as the first-line therapy for hypertensive patients with diabetes [35-39]. This indication is based not only on their effectiveness in reducing BP without deterioration of glucose and lipid metabolism, but mainly on their «renal protective» properties. A recent study verified a better preservation of renal function with the ACE inhibitor enalapril than with beta-blocker metoprolol [39]. Actually, the beneficial effects of ACE inhibition in diabetic nephropathy are observed independently of changes in BP and appear to depend on its intrarenal effects. Glomerular capillary hypertension and increased glomerular basement membrane permeability occur during the development of renal disease. ACE inhibitors were able to ameliorate glomerular hypertension in experimental models and to reduce proteinuria[35]. This is achieved by decreasing efferent arteriolar resistance to a greater extent than afferent resistance, determining lower perfusion pressure and single nephron glomerular filtration rate. Studies in humans confirmed the uselfulness of these agents in slowing the progression of nephropathy[37-39] and proposed an action on intrinsic membrane properties of the glomerular barrier, enhancing the size selectivity to macromolecules[38]. Our experience with different antihypertensive agents showed that captopril in hypertensive IDDM patients reduced mean BP and albuminuria without significant changes in renal hemodynamic parameters[21]. Nor there was correlation between the changes in BP and those in albumin excretion. This lack of correlation contrasted with the correlations observed for hydrochorthiazide and nitrendipine. In accordance to others[40]. Our data suggested that captopril lowers albumin excretion by mechanism that are not as closely related to BP reduction. Therefore, particularly in microalbuminuric IDDM patients, in whom the nephropathy is the main cause of increased morbidity and mortality, ACE inhibitors have been recommended in order to prevent progression of such complication, even in absence of hypertension[41]. The favorable metabolic profile of ACE inhibitors, associated with preliminary observations of the reversal of left ventricular hypertrophy[42] and also improvement of insulin resistance[25], make these drugs also attractive for NIDDM hypertensive patients. Unfortunately, the high cost of this therapy may limit compliance in a number of patients. Orthostatic hypotension secondary to diabetic autonomic neuropathy may be aggravated with ACE inhibition. The presente of renal failure represents another limitant factor due to its potassium retaining effect. Long-term prospective studies comparing the impact of ACE inhibitors with other antihypertensive drugs are needed to confirm advantages of the former in the treatment of hypertensive patients with diabetes.

Neverthless they seem very promissing drugs for diabetic patients.

d) *Calcium channel blockers*

As well as the others, CC8 are suitable for initial therapy in diabetic hypertensive patients. The blockade of calcium influx to cells induces systemic and renal vasodilation. Besides lowering BP this class of drugs has been used for patients with ischaemic heart disease even with renal impairment. In contrast to other vasodilators, they cause natriuresis and diuresis. There are controversies concerning the effects of the CCB on the renal hemodynamics. Particularly in diabetes, studies showed variable effects on renal plasma flow, glomerular filtration rate and albumin excretion that may be related to the time in the disease process [11,43-45]. In our experience, in IDDM patients nitrendipine reduced BP and urinary protein excretion whose percentage falls were correlated [21]. Renal plasma flow increased and glomerular filtration rate decreased and both filtration fraction and renal vascular resistance were reduced. Our data are in accordance to previous suggestion that these drugs dilate afferent arteriole without change efferent arteriollar resistance [46]. Other studies similar to ours have also observed a antiproteinuric effect, indicating that the

systemic BP fall is the main determinant of the decrease in urinary protein excretion induced by the CCB [11, 44]. However, some reports have indicated that CCB may not aher urinary albumin excretion and may even increase it [43,45]. Longer studies with a greater number of patients are necessary to clarify these aspects. Because of the effectiveness, of this class of antihypertensive drugs and lack of deleterious effect on glucose and lipoprotein metabolism, they have been considered a first-line therapy for hypertension in NIDDM or IDDM. They became a very interesting option in the diabetic patient with coronary artery disease associated with left ventricular hypertrophy.

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