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Research Article

IMPACT OF ANTIHYPERTENSIVE DRUGS ON GLYCEMIC CONTROL

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ABSTRACT

The effect of antihypertensive agents on glucose metabolism varies according to its type. Different anti hypertensive drugs have different effect on glucose metabolism. Numerous studies have shown that some class of anti hypertensive agents can promote the development of new onset of type-2-diabetes mellitus and also worsen the existing diabetes mellitus. Hypertensive patients on Thiazide diuretic therapy have shown to develop glucose intolerance and new onset diabetes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB's) have shown a positive effects on glycemic control through a large variety of mechanisms associated to the inhibition of angiotensin thereby not promoting the new onset of diabetes mellitus. A higher incidence of new onset diabetes mellitus was also found with diuretics and/ or beta blockers. Therefore the metabolic outcomes of various antihypertensive drugs should be understood; otherwise not only the disease itself, but also antihypertensive therapies might promote both the development of new onset diabetes and macro, micro complications of diabetes. Hence anti hypertensive agents should be carefully selected as to not further deteriorate an already at risk glucose homeostasis in hypertensive patients.

INTRODUCTION

Diabetes and hypertension are common diseases of great importance and their management requires attention, both clinically and pharmacologically. Hypertension is extremely common co morbidity in patients with type 2 diabetes mellitus. The presence of hypertension in patients with type 2 diabetes is particularly destructive because of their strong linkage with cardiovascular diseases (CVD), stroke, progression of renal disease and diabetic nephropathy[1]. Even it is very hard to control hypertension in diabetic hypertensive patients and hence antihypertensive combination therapy is required to take control over the elevated blood pressure[2]. In type II diabetics also, hypertension and diabetes are commonly associated and here obesity is the factor which could produce a spurious association[3]. Despite these possible confounding factors, most studies which have taken obesity and nephropathy into account still report a strong association between hypertension and diabetes, although this remains a controversial point[4]. In any event, a large number of patients with both hypertension and diabetes do exist. These patients have two major risk factors for cardiovascular disease and it is important, therefore, to establish guidelines for their management. Furthermore, we now have information that controlling blood pressure in diabetics is positively beneficial as far as the progression of nephropathy is concerned. Balanced against this, however, is the problem that most available antihypertensive drugs are known to worsen glycemic control and we have no comparative data to guide us on which drugs we should use[5]. The various classes of antihypertensive drugs have different effects on blood glucose metabolism. Numerous analyses have demonstrated that antihypertensive therapies promote the development of type-2-diabetes mellitus. Antihypertensive agents, such as β-blockers (BB) and thiazide diuretics have shown negative effects on blood glucose[6]. Studies have shown that the application of angiotensin converting enzyme inhibitors 1 (ACEI's) and angiotensin receptor blockers (ARB's) lead to less new-onset diabetes (NOD) compared to beta-blockers, diuretics and placebo. The metabolic outcomes of various antihypertensive drugs should be understood; otherwise not only the disease itself, but also antihypertensive therapies might promote the development of new onset diabetes[6]. Hence anti hypertensive agents should be carefully selected as to not further deteriorate an already at risk glucose homeostasis in hypertensive patients.

Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers

Studies have shown that ACE inhibitors are associated with a lower incidence of new-onset diabetes mellitus type2 in

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hypertensive patients. ACE inhibitors prevent or delay microvascular and macrovascular complications of diabetes and are recommended as first-line antihypertensive agents in diabetic hypertensive patients. A retrospective study evaluated the effect of enalapril and showed that it significantly reduced the incidence of diabetes compared with placebo[7-9].Similar were the results of another meta-analysis of randomized clinical trials that showed ACE inhibitors had a smaller incidence of new onset T2DM compared with control groups[10].Treatment with ARBs has also been associated with an overall beneficial effect on glucose homeostasis[11]. The losartan intervention for endpoint reduction (LIFE) in hypertension study was a double-blinded, randomized, parallel-group trial in patients aged between 55-80 years with hypertension and LV hypertrophy. Patients were randomized to losartan or atenolol based antihypertensive treatment for a mean follow-up of 4.8 years. The study showed that losartan treatment was associated with a reduction of new-onset T2DM compared with the control group[12]. Another prospective, double-blind, randomized trial recruited hypertensive patients with additional CV risk factors. The study subjects were randomized to either amlodipine or valsartan based regimen. The study showed that valsartan based group had a smaller incidence of new-onset T2DM compared with the amlodipine group[13]. The rennin angiotensin system plays the key role in both the pathogenesis of hypertension and glucose homeostasis. Bradykinin has a beneficial role in glucose homeostasis[14-15]. The ACE other than converting angiotensin I to angiotensin II, it can also decrease bradykinin levels. Moreover, ACE promotes the degradation of bradykinin to inactive fragments through a kininase II- mediated mechanism. As a result, ACE inhibitors can increase bradykinin levels. Bradykinin has shown to promote insulin sensitivity at the skeletal muscle level[16]. Glucose transporter type 4, is the principle glucose transpoter that mediate insulin-stimulated glucose transport into muscle and adipose tissue and it plays a key role in the regulation of glucose homeostasis. Angiotensin decreases GLUT-4 translocation to the cell membrane. As a result the RAAS inhibition could promote insulin sensitivity. Angiotensin converting enzyme inhibitors has shown to improve vascular function and insulin-mediated vascular responses[17]. ACE inhibitors may also have direct beneficial effects on pancreatic β cells. In addition to this inhibition of angiotensin converting enzyme can lead to vasodilation of blood vessels. This vasodilation results in the increment of total perfused area and thus increases glucose uptake and insulin sensitivity[18]. The activation of the sympathetic nervous system has also been associated with insulin resistance.

Calcium Channel Blockers

Calcium antagonists are used increasingly in the treatment of hypertension. Many investigations have focused on the effect of calcium channel blockers on glucose tolerance because calcium influx is an essential step in insulin release [19]. This beneficial effect of CCB's may be due to partial activation of the PPARγ that plays a major role in glucose metabolism.[20-21].

Beta Blockers

A number of studies have have showed that treatment with β-blockers has a disadvantageous effect on glucose homeostasis. In the Atherosclerosis Risk in Communities study β-blockers led to an increased risk for new onset T2DM. In a meta-analysis of patients with hypertension treated with beta-blocker therapy resulted in a 22% increased risk for new-onset T2DM [22]. Non-vasodilating beta-blockers such as atenolol and metoprolol have reported to worsen insulin sensitivity. Potential mechanisms through which these beta-blockers impair glucose metabolism include decreased exercise, reduced skeletal muscle blood flow, decreased islet cell insulin secretion and the antagonistic effects of blockade of the beta-2 receptor on insulin metabolic signaling. Insulin sensitivity and glycemic control may be affected by several actions of beta blockers[23]. It blocks pancreatic beta-2 receptors there by inhibiting insulin secretion. This inhibits insulin secretion and thus results in an impaired glucose metabolism leading to hyperglycemia. This effect is more commonly seen in non selective beta blockers but can also been seen with higher dose of selective beta blocker. Newer beta blockers which cause vasodilatation may not have the deleterious effects on insulin sensitivity and glucose metabolism as like described above [24].

Diuretics

A number of studies have shown that diuretic treatment for the hypertension has a negative effect on glucose homeostasis[25]. Also, a meta-analysis with non diabetic people evaluated the effects of various antihypertensive drug classes on diabetes incidence[26]. Treatment with diuretic has an increased association with the increased risk for new onset diabetes compared with other antihypertensive treatments as well as the placebo[27]. A long-term cohort study with initially untreated hypertensive subjects evaluated new-onset diabetes incidence with chlorthalidone seems to be different from the rest of the thiazide diuretics class and has a different chemical structure compared with the rest of thiazide diuretics as well as the ability to inhibit carbonic anhydrase[28]. Carbonic anhydrase activity is also directly proportional to the increasing blood glucose concentration. As a result, the thiazide diuretics may have a less favorable metabolic profile compared to that of the other chlorthalidone[29]. Recently, Verdecchia *et al*., reported an increased rate of new onset of diabetes in patients receiving low-dose thiazides but not other antihypertensive agents, including newer beta blockers[30-32].Some findings suggest that the probability of worsening glucose metabolism and the development of new diabetes after thiazide initiation is associated with increasing body mass index[33]. The possible mechanisms through which thiazide diuretics affecting glucose homeostasis still remains unclear. Some studies says that hypokalemia is least contributory though it can decrease insulin secretion by β cells in response to glucose[34]. It is of interest also that several other syndromes that are characterized by hypokalemia have been shown to be associated with glucose intolerance. These include primary hyperaldosteronism, Bartter's syndrome, and Cushing's syndrome. Several other studies showed proved that the potassium depletion in healthy subjects were associated with a decreased insulin response to glucose, while tissue sensitivity to insulin was unchanged[35]. Moreover, a decrease in magnesium can also be seen with diuretic treatment[36]. This could also contribute to the negative effects of diuretics on glucose homeostasis, as decline in magnesium level is an independent predictor ofT2DM. Thiazide treatment has also been associated with the visceral fat redistribution, liver fat accumulation and shows low-grade inflammation, which would in turn increase the risk of NOD. Therefore the current position is that the thiazide diuretics do

induce glucose intolerance, especially in diabetic patients and also in healthy persons[37]. There is good evidence to suggest that changes in body potassium are at least contributory to this effect, but whether this effect is predominantly due to insulin deficiency or to insulin resistance still remains unknown.

CONCLUSION

This review concentrated on the effect of various antihypertensive drugs on glycemic control. Antihypertensive treatment has a significant influence on the incidence of diabetes mellitus, and the incidence is higher for patients treated with diuretics or beta blockers than for patients treated with CCB's, ACEI's and ARB's. Currently, the main recommendation is that after the initiation of antihypertensive therapy in a diabetic patient, he/she should be reassessed not only for side effects but for the biochemical indexes of glycemic control. The coexistence of hypertension and type 2 diabetes mellitus increases the risk of microvascular and macrovascular complications, including coronary artery disease, stroke, peripheral vascular disease, nephropathy, neuropathy, and retinopathy. Hence identifying hypertensive patients at increased risk of developing diabetes and choosing appropriate medications would minimize this risk is of major complications.

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