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Hypertension management in diabetic patients

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Abstract. – Hypertension and diabetes are becoming increasingly common. Clinical trials have demonstrated the importance of tight blood pressure control among patients with diabetes. However, little is known regarding the management of hypertension in patients with coexisting diabetes. Most patients with both disorders have a markedly worsened risk for premature micro vascular and macro vascular complications. The appropriate management of the hypertension seen in almost 70% of patients with type 2 diabetes mellitus remains controversial. However, over the past few years, many randomized, controlled trials have provided guidance for more effective therapy. These trials have established the need for a lower goal blood pressure (<130/80 mm Hg) than has previously been recommended. To achieve therapy goals, multiple antihypertensive drugs are usually needed.

Key Words:

Hypertension, Diabetes mellitus, Macrovascular, Microvascular, Cardiovascular disease.

Introduction

Hypertension (defined as a blood pressure ≥140/90 mmHg) is an extremely common condition in diabetes, affecting ~20-60% of patients with diabetes, depending on obesity, ethnicity, and age. Hypertension is a condition in which blood pressure is high. It can be caused by genetics, diet as well as stress. It is associated with significant health problems such as stroke and heart attack[1,2]. The following clinical levels of hypertension[1,2] have been described by The National Heart, Lung, and Blood Institute:

Stage one hypertension: consistent (i.e., two or more consecutive) readings of 140-159/90-99 mmHg.

Stage two hypertension: consistent readings of 160/100 mmHg or higher.

Pre-hypertension: consistent readings of 120-139/80-89 mmHg.

Diabetes mellitus often simply referred to as diabetes is a condition in which a person has a high blood sugar level, either because the body doesn't produce enough insulin, or because body cells don't properly respond to the insulin that is produced[3]. There are many types of diabetes, the most common of which are[4]:

Type 1 diabetes: results from the body's failure to produce insulin, and presently requires the person to inject insulin.

Type 2 diabetes: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency.

Gestational diabetes: it is when pregnant women, who have never had diabetes before and have high blood glucose level during pregnancy. It may precede development of type 2 diabetes mellitus.

Other forms of diabetes mellitus include *congenital diabetes*, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, *steroid diabetes* induced by high doses of gluco-corticoids, and several forms of *monogenic diabetes*.

How are Diabetes and Hypertension Related?

Diabetes and high blood pressure tend to occur together because they share certain physiological traits. High blood pressure is a dangerous disease that becomes even more problematic in the setting of diabetes. Unfortunately, many people with diabetes are also affected by high blood pressure, and

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the two diseases commonly occur together[5-7]. Diabetes and high blood pressure occur together so frequently that they are officially considered to be "comorbidities" (diseases likely to be present in the same patient). In the case of diabetes and high blood pressure, these effects include:

Increased Fluid Volume – Diabetes increases the total amount of fluid in the body, which tends to raise blood pressure.

Increased Arterial Stiffness – Diabetes can decrease the ability of the blood vessels to stretch, increasing average blood pressure.

Impaired Insulin Handling – Changes in the way the body produces and handles insulin can directly cause increases in blood pressure.

Apart from above factors the two diseases are likely to occur together simply because they share a common set of risk factors. Some important shared risk factors are:

Body Mass – Being overweight significantly increases the risk of both diabetes and high blood pressure.

Diet – High fat diets rich in salt and processed sugars are known to contribute to the development of organ problems that can lead to both diabetes and high blood pressure.

Activity Level – A low level of physical activity makes insulin less effective (which can lead to diabetes) and can contribute to the development of stiff blood vessels, increasing the risk of high blood pressure.

The well-studied *example* of the self-reinforcing relationship between diabetes and high blood pressure takes place in the kidneys. The kidneys are the body's most important long-term blood pressure regulator. By balancing the amount of salt and potassium in the body, the kidneys ultimately control how much fluid is excreted as urine. This fluid regulating function helps to modulate long-term blood pressure by physically controlling how much liquid is present in the blood vessels.

Relationship Between Diabetes and Hypertension

Figure 1 shows the interrelationship between the hyperglycemia and the hypertension through the intervention of insulin resistance, a common link between the two diseases.

Statistical Relationship

Individuals with diabetes are at a much greater risk for developing. Hypertension is twice as common in those with diabetes as in non diabetic individuals[1,2,8].

Physical Relationship

Diabetes causes hyperinsulinemia and raises the risk of hypertension. This condition increases the amount of sodium that the body absorbs. It also promotes the stimulation of the sympathetic nervous system. This is thought to cause changes in blood vessel structure, which affects the function of the heart and blood pressure[1,2,8].

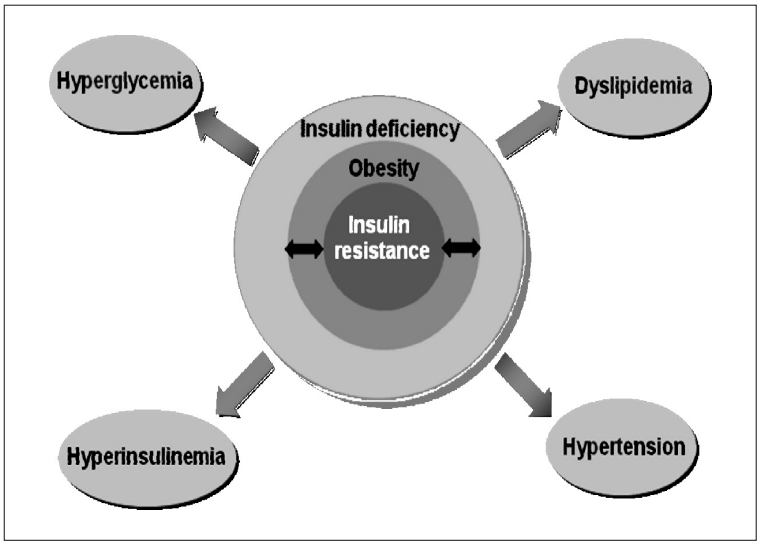

Figure 1. Metabolic syndrome.

Obesity

Metabolism is related to obesity, which is related to diabetes, which is related to hypertension. Reducing in weight can often lower blood pressure. This lowering of hypertension symptoms is associated with a decrease in the symptoms of diabetes[1,2,8].

Evidences

Hypertension as a Risk Factor for Complications of Diabetes

Diabetes increases the risk of coronary events two fold in men and four fold in women. This increase is due to the frequency of associated cardiovascular risk factors such as hypertension, dyslipidemia and clotting abnormalities. People with both diabetes and hypertension have approximately twice the risk of cardiovascular disease as non-diabetic people with hypertension. Hypertensive diabetic patients are also at increased risk for diabetes-specific complications including retinopathy and nephropathy[1,2].

Evidence for Target Levels of Blood Pressure in Patients with Diabetes

The UK Prospective Diabetes Studies (UKPDS) and the Hypertension Optimal Treatment (HOT) trial both demonstrated improved outcomes, especially in preventing stroke, in patients assigned to lower blood pressure targets. Optimal outcomes in the HOT study were achieved in the group with a target diastolic blood pressure of 80 mmHg. Randomized clinical trials demonstrate the benefit of targeting a diastolic blood pressure of ≤80 mmHg. Epidemiological analyses show that blood pressures ≥120/70 mmHg are associated with increased cardiovascular event rates and mortality in persons with diabetes. Therefore, a target blood pressure goal of <130/80 mmHg is reasonable if it can be safely achieved. Achieving lower levels, however, would increase the cost of care as well as drug side effects and is often difficult in practice[1,2].

Types of Hypertension in Diabetes Mellitus

1. Essential hypertension
2. Hypertension consequent to nephropathy
3. Isolated systolic hypertension
4. Supine hypertension with orthostatic fall[9]

Guidelines for the Management of Hypertension

Effective blood pressure control is an important goal for diabetic patients. The patients who suffer from both diabetes and hypertension have greater chances of developing cardiovascular disorder[10]. The following guidelines must be considered for the management of hypertension in diabetic patients:

Measurement of Arterial Blood Pressure: The object of identifying and treating high blood pressure is to reduce the risk of cardiovascular disorder and associated morbidity and mortality. It is, therefore, necessary to provide a classification of blood pressure in adults so as to identify the high risk individuals and to provide guidelines for treatment and follow up. Arterial blood pressure measured in the sitting position should be considered as ideal[11].

Systolic and Diastolic Pressure Target Values: The level to which blood pressure should be reduced in a diabetic hypertensive patient has not been known[12]. There are no specific guidelines on the exact values for hypertension control in diabetes. A number of epidemiological studies suggest an inverse relationship exist between calcium, magnesium, potassium intake and blood pressure level[13-15]. Most of these studies are cross-sectional, but none of these studies has analyzed diabetic patients separately from the general hypertension population. There are no randomized clinical trials on magnesium supplementation in diabetic subjects with hypertension.

Screening and Initial Evaluation: All patients with diabetes should have blood pressure measured at the time of diagnosis and at each scheduled diabetes visit[13]. Initial assessment of a hypertensive diabetic patient should include a complete medical history with special emphasis on cardiovascular risk factors and the presence of diabetes complication. The physical exam should include height, weight, and careful evaluation of arterial circulation. Initial laboratory examination should include serum creatinine, electrolytes, fasting lipid profile, and urinary albumin excretion[16].

Behavioral Treatments of Hypertension: Dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension[17,18]. Weight reduction can reduce blood

pressure independent of sodium intake and can also improve blood glucose and lipid levels[19]. Sodium restriction has not been tested in the diabetic population in controlled clinical trials. Reductions in daily sodium intake to levels of 10-20 mmol (230-460 mg) per day have resulted in decreases in systolic blood pressure of 10-12 mmHg[17]. Smoking cessation and moderation of alcohol intake are also recommended to reduce blood pressure[20-22].

Treatment Goals

In the setting of diabetes, the target blood pressure is <130/80. Significant improvements in long term cardiovascular and kidney health do not become apparent until blood pressure is reduced to this level. Because it is difficult to reduce blood pressure to this level, it is a recommendation usually reserved only for specific patients[23-25].

Drug Therapy

Drug therapy is a necessary step for most patients during treatment. Vast amounts of research have been done in an effort to determine which drug or drug combination is the "best" for treating high blood pressure in patients with diabetes. The best drugs to use in the setting of diabetes are:

Angiotensin Converting Enzyme (ACE) Inhibitors: ACE inhibitors have proved beneficial in patients who have myocardial infarction or congestive heart failure, or who have diabetic renal disease[10]. ACE inhibitor therapy results in 20 to 30 percent decrease in the risk of stroke, coronary heart disease, and major cardiovascular events[26,27]. ACE inhibitors are found to be more beneficial when compared with other antihypertensives in the reduction of acute myocardial infarction, cardiovascular events, and mortality. *Captopril* and *atenolol* are similar in terms of reduction in microvascular and macrovascular complications[28].

Diuretics: Thiazide diuretics have been shown to benefit patients with diabetes and systolic hypertension. *Chlorthalidone* therapy is effective in preventing major cerebrovascular and cardiovascular events in older non-insulin-treated patients with diabetes and isolated systolic hypertension. Lower dosages of thiazides (e.g., hydrochlorothiazide) are generally well tolerated and not associated with adverse metabolic effects[31]. Thiazide diuretics are not as effective in patients with renal insufficiency; in such patients, *loop diuretics* are preferred.

Calcium Channel Blockers (CCB): Controversy exists regarding the use of CCBs, particularly the *dihydropyridines* (e.g., amlodipine, nifedipine) in treating hypertension in patients with diabetes. The combination of an ACE inhibitor and a dihydropyridine CCB has been shown to reduce proteinuria[2]. The *nondihydropyridine* CCBs (e.g., verapamil) demonstrate reductions in cardiovascular risk when used as monotherapy. Combining a nondihydropyridine CCB with an ACE inhibitor in hypertensive patients with diabetes is associated with greater reductions in proteinuria than if either agent was used individually[2,32].

Angiotensin II Receptor Blockers (ARB): *Candesartan* and *lisinopril* are used to treat patients with type 2 diabetes, hypertension, and microalbuminuria[33]. Candesartan is as effective as lisinopril in blood pressure reduction and minimization of microalbuminuria[34-35]. Losartan therapy produced a renoprotective effect independent of its blood-pressure-lowering effect in patients with type 2 diabetes and nephropathy[35,36]. *Irbesartan* is found to be renoprotective in patients with type 2 diabetes who have microalbuminuria. *Valsartan* lowers urine albumin excretion to a greater degree than *amlodipine* in type 2 diabetic patients with microalbuminuria[37].

Beta Blockers: Traditionally, the use of beta blockers in patients with diabetes has been discouraged because of adverse metabolic effects and the masking of hypoglycemic symptoms. There is no difference in hypoglycemic episodes in patients treated with *atenolol* compared with *captopril*, but the mean weight gain in the atenolol group was greater[28]. Cardio selective beta blockers are preferred over the non-selective type because they are associated with less blunting of hypoglycemic awareness and less elevation of lipid and glucose levels. The alpha beta blocker *carvedilol* causes fewer alterations in lipid and glucose levels compared with traditional beta blockers[38]. Beta-blocker therapy can be advantageous in many patients with diabetes because of its proven ability to decrease cardiovascular morbidity and mortality in persons with atherosclerotic heart disease[39].

Renin Inhibitors: A new and promising approach in rennin angiotensin aldosterone system blockade has been started with the development of first direct renin inhibitor, *aliskiren*, recently approved by US Food and Drug Administration (FDA) for the treatment of hypertension in diabetic patients. Aliskiren is generally well tolerated and, in contrast to ACE inhibitors, it does not induce accumulation of substance P or bradykinin. Therefore, side effects such as cough and angioedema are very rare. It has demonstrated a favorable safety and tolerability profile alone or in combination with other drugs[39]. Aliskiren monotherapy demonstrated significant, dose-dependent antihypertensive effects in several placebo-controlled clinical trials[40]. Renin inhibition seems an interesting new approach for preventing the progression of chronic kidney disease[41].

Combination Therapy

Diabetes and hypertension constitute a particularly dangerous combination with respect to cardiovascular morbidity and mortality. A significant increase in systolic blood pressure in any age group leads to significant increase in cardiovascular disease. Therefore, it is necessary to reduce blood pressure[42]. Most patients with hypertension and diabetes require more than one agent to attain adequate blood pressure control. In the HOT (Hypertension Optimal Treatment) trial, 68% of patients were maintained on combination antihypertensive therapy. The combination of ACE inhibitors and CCBs is associated with a reduction in cardiovascular events and protein-urea[2,43-46]. The combination of a dihydropyridine and a nondihydropyridine CCB has been shown to have a synergistic blood-pressure-lowering potential[47]. Caution should be used with the combination of nondihydropyridine CCBs and beta blockers because of the potential for additive negative cardiac inotropic effects. Combinations of beta blockers and ACE inhibitors have shown few additive effects on blood pressure when used in patients with a pulse rate of less than 84 beats per minute[48]. The final phase of the CALM (candesartan and lisinopril microalbuminuria) study examined combination treatment with candesartan and lisinopril[33].

The following steps are required for combination treatment of hypertension in diabetic patients:

- Patients with a systolic blood pressure of 130-139 mmHg or a diastolic blood pressure of 80-89 mmHg must be given lifestyle/behavioral therapy for a period of 3 months and then should be treated pharmacologically with agents that block the renin-angiotensin system.
- In addition to lifestyle/behavioral therapy patients with hypertension should receive drug therapy.
- Multiple drug therapy is generally required to achieve blood pressure targets.
- For those having blood pressure ≥ 140/90 should be given drug to reduce cardio-vascular disorder events.
- All patients with diabetes and hypertension should be treated with a regimen that includes an ACE inhibitor or ARB. If one is not tolerated, the other should be given. If blood pressure targets are to be achieved, a thiazide diuretic should be added.
- If ACE inhibitors or ARBs are used, renal function and serum potassium levels should be monitored.
- 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, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria.
- In those with type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency, an angiotensin receptor blocker should be strongly recommended.
- In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications.
- Patients not achieving target blood pressure on three drugs, including a diuretic and patients with a significant renal disease should be referred to a physician experienced in the care of patients with hypertension[1,2].

Non-Drug Therapy

This therapy mainly includes weight loss, salt restriction, dietary changes, quitting smoking, limiting alcohol intake, etc[29-31]. In patients without diabetes, strict adherence to these rules very often leads to significant drops in blood pressure so much that drug therapy may not be needed. In the Dietary Approaches to Stop Hypertension trial, lifestyle modifications such as exercise and a diet low in salt and high in potassium have clear-

ly been shown to decrease blood pressure[49]. Excessive sodium intake is particularly deleterious in patients with diabetes because it may decrease the antihypertensive effects of medications and their beneficial effects on protein urea[50]. Weight loss and exercise can help to lower blood pressure and may also improve glycaemic control and insulin sensitivity.

Conclusion

Control of hypertension and maintenance of ideal blood pressure is the moot point that would benefit the diabetic patient most. Pharmacists must become more vigilant about current guidelines for the treatment of patients with concomitant hypertension and type 2 diabetes mellitus. Strategies such as patient education and medication assessment can help to optimize care for these patients and slow the progression to diabetic nephropathy. Many patients with diabetes mellitus and hypertension are not been treated according to guidelines. Specific risk factors determined may aid in identifying patients at high-risk for inadequate treatment. Patient and education provider, public health approaches, and health system changes are needed to address these issues. As the population grows older and continues to gain weight, diabetes and hypertension will become even more common. It is to be hoped that an approach similar to that outlined here can limit their serious consequences.

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