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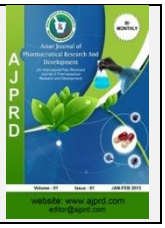

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Review Article

Review on Relationship between Hypertension and Diabetes with their Medications

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ABSTRACT

Hypertension and diabetes are two very common chronic conditions in the modern world, and they are closely related. Hypertension is a condition in which blood pressure is consistently high, and diabetes is a condition in which blood sugar levels are abnormally high. Both conditions increase the risk of cardiovascular disease, kidney disease, and many other complications. Studies have shown that many people with high blood pressure also have diabetes, and vice versa.In conclusion, hypertension and diabetes are interrelated conditions that can cause serious health problems for many people in the modern world. People with diabetes are more likely than the general population to develop high blood pressure because diabetes can cause damage to blood vessels or trigger an inflammatory response within the blood vessels, which can lead to stiffness of the blood vessels.Conversely, high blood pressure makes diabetes worse. When hypertension persists, the burden on the blood vessels continues to increase, putting the kidneys and heart of diabetics at greater risk.The bottom line is that these two conditions end up interacting with each other and promoting different complications.This approach will go a long way toward preventing the development of hypertension and diabetes and leading a healthy life.

Keywords: Hypertension, Diabetes, Combined Therapy, Medication

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INTRODUCTION

High blood pressure and diabetes are two closely related chronic conditions. Although they are independent health issues, they are more likely to occur together and can increase the risk of one another.Hypertension and diabetes can be promoted by common lifestyle factors, such as obesity, physical inactivity, smoking, unbalanced diet, and excessive alcohol consumption[1]. These lifestyle factors increase the likelihood of developing both conditions at the same time.Diabetes, especially type 2 diabetes, is associated with insulin resistance. Having insulin resistance leads to high blood sugar levels, which can damage blood vessels and cause high blood pressure. Insulin resistance itself can also play a role in raising blood pressure.Both high blood pressure and diabetes adversely affect the health of blood vessels. High blood pressure damages blood vessels by putting excessive pressure on the walls of blood vessels, while diabetes can damage the lining of blood vessels due to high blood sugar. As this damage accumulates, the risk of cardiovascular disease increases significantly[2].

In people with diabetes, high blood pressure increases the risk of developing complications of diabetes, especially kidney disease (diabetic nephropathy), retinal disease (diabetic retinopathy), and cardiovascular disease. People with diabetes who have high blood pressure have a higher risk of death from cardiovascular disease. Therefore, it is very important to manage both hypertension and diabetes simultaneously.

Both conditions can lead to serious complications, which can be life-threatening, if not properly managed. Therefore, it is important for people with hypertension and diabetes to manage their conditions through lifestyle modifications and, if necessary, medication.When hypertension and diabetes co-occur, the risk of cardiovascular disease and other

complications increase significantly, so early diagnosis and consistent management are essential[3].

Close Look on Hypertension

Blood pressure is the force that blood exerts on the walls of blood vessels. When reading blood pressure, it is divided into systolic (highest) and diastolic (lowest) readings. Systolic blood pressure is the pressure on the blood vessels when the heart contracts and pushes blood out, and diastolic blood pressure is the pressure on the blood vessels when the heart expands (relaxes) and takes in blood.

High blood pressure is defined as a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher in adults 18 years of age or older[4]. Hypertension can be categorized into two main types: secondary hypertension, which is caused by a known underlying medical condition, and essential (primary) hypertension, which has no known underlying medical condition. About 95% of all people with hypertension have essential hypertension[5].

The underlying cause of essential hypertension is not clear, but it is thought to be caused by an increase in cardiac output (the amount of blood pumped by the heart in one minute) or an increase in peripheral vascular resistance. Risk factors associated with hypertension include a family history of hypertension, alcohol consumption, smoking, advanced age, lack of exercise, obesity, a salty diet, and environmental and psychological factors such as stress.Hypertension is caused by both neurogenic factors through the sympathetic nervous system and humoral factors through the renin-angiotensin mechanism. However, heredity, smoking, being male, and aging are factors that predispose to hypertension [6].

More than 90% of hypertension is essentially of unknown cause. The remaining 5-10% is secondary hypertension, which has a clear cause. Essential hypertension, which accounts for the majority of hypertension cases, is not caused by a single factor. It is caused by a combination of factors, the most common of which is genetics (family history), but other factors include aging, obesity, a salty diet, lack of exercise, and stress.

The factors that contribute to high blood pressure are summarized below.Family history of cardiovascular disease (genetics), Smoking, Hyperlipidemia, Diabetes, Age (after 60), Gender (men and postmenopausal women), Dietary factors: excessive intake of Na, fat and alcohol, insufficient intake of K, Mg, Ca, and Medication factors: oral contraceptives, antacids, anti-inflammatory drugs, appetite suppressants[7].

1. Renin-Angiotensin-Aldosterone System (RAAS)

The kidneys release renin in response to low blood pressure, low sodium levels, or sympathetic nervous system activation.Renin converts angiotensinogen (produced by the liver) to angiotensin I, which is then converted to angiotensin II by the angiotensin-converting enzyme (ACE) in the lungs. Angiotensin II is a potent vasoconstrictor, increasing blood pressure.Angiotensin II stimulates the adrenal glands to secrete aldosterone, which promotes sodium and water retention by the kidneys, increasing blood volume and blood pressure[8].

2. Sympathetic Nervous System Activation

Chronic activation of the sympathetic nervous system, often due to stress, leads to increased heart rate and vasoconstriction, both of which raise blood pressure.Increased levels of norepinephrine and epinephrine from sympathetic nerve endings cause vasoconstriction and increase cardiac output[9].

3. Endothelial Dysfunction

The endothelium (lining of blood vessels) produces nitric oxide, a vasodilator. Dysfunctional endothelium results in reduced nitric oxide availability, leading to vasoconstriction and increased peripheral resistance.Endothelial cells may produce more endothelin, a potent vasoconstrictor, contributing to higher blood pressure[10].

4. Renal Mechanisms

The kidneys regulate blood pressure by controlling blood volume. Impaired kidney function can lead to excessive sodium and water retention, increasing blood volume and pressure.A defect in the pressure-natriuresis mechanism, where higher blood pressure should lead to increased excretion of sodium, can result in sodium retention and volume expansion[11].

5. Hormonal Factors

Often seen in obesity and diabetes, insulin resistance can lead to hypertension by promoting sodium retention and activating the sympathetic nervous system.This hormone, which is elevated in obesity, can stimulate the sympathetic nervous system and contribute to hypertension[12].

6. Vascular Remodeling

Chronic high blood pressure causes the walls of blood vessels to thicken (hypertrophy), reducing the lumen size and increasing resistance.The elasticity of blood vessels decreases with age and certain conditions, leading to increased peripheral resistance and higher systolic blood pressure[13].

Close look on Diabetes

The molecular mechanisms of diabetes, both Type 1 and Type 2, involve complex pathways that ultimately lead to impaired glucose metabolism. Here's a breakdown of the key molecular processes in each type of diabetes:

1. Type 1 Diabetes

Type 1 diabetes is primarily caused by an autoimmune response in which T-cells (particularly CD8+ cytotoxic T cells) mistakenly recognize and attack the insulin-producing β-cells in the pancreas. This is due to the presence of autoantigens such as insulin, glutamic acid decarboxylase (GAD65), and islet antigen-2 (IA-2)[14].The autoimmune attack involves the activation of the T-cell receptor (TCR) upon recognizing β-cell antigens presented by MHC class I molecules. This leads to the release of cytokines like IFN-γ, TNF-α, and IL-1β, which contribute to β-cell apoptosis via pathways such as the Fas-FasL interaction and the mitochondrial apoptotic pathway.Over time, the loss of β-cells leads to a significant reduction in insulin production,

and without insulin, cells cannot uptake glucose, leading to hyperglycemia[15].

2. Type 2 Diabetes

Impaired Insulin Signaling: In Type 2 diabetes, insulin resistance is a key feature. Normally, insulin binds to the insulin receptor on the cell surface, activating a signaling cascade through the PI3K-Akt pathway. This cascade promotes glucose uptake by translocating the GLUT4 glucose transporter to the cell membrane. However, in T2D, this signaling pathway is impaired[16].

Several factors contribute to insulin resistance:

Insulin receptor substrate (IRS) proteins, which are critical for transmitting signals from the insulin receptor, are abnormally phosphorylated on serine residues rather than tyrosine. This impairs their ability to activate downstream pathways.Adipose tissue in obesity often produces pro-inflammatory cytokines like TNF-α and IL-6, which activate kinases such as JNK and IKK. These kinases phosphorylate IRS on serine residues, further contributing to insulin resistance[17].

Excessive free fatty acids and intracellular lipids in liver and muscle cells can interfere with insulin signaling by activating stress kinases (e.g., PKCθ) and causing mitochondrial dysfunction.Compensatory Hyperinsulinemia: Initially, β-cells compensate for insulin resistance by producing more insulin. However, chronic hyperglycemia and elevated free fatty acids can induce β-cell stress and apoptosis through mechanisms like ER stress, oxidative stress, and amyloid deposition (from islet amyloid polypeptide)[18].

Chronic high glucose levels (glucotoxicity) and elevated free fatty acids (lipotoxicity) contribute to β-cell dysfunction by inducing oxidative stress and impairing mitochondrial function, leading to reduced insulin secretion[19].

3. Common Molecular Aspects

Persistent hyperglycemia results from the inability of insulin to effectively lower blood glucose levels. This condition leads to glycation of proteins (advanced glycation end-products, AGEs), which can damage tissues and organs, contributing to diabetic complications[20].

Mitochondria play a crucial role in both insulin secretion and action. In T2D, mitochondrial dysfunction in β-cells and insulin-responsive tissues (like muscle and liver) leads to impaired energy metabolism, contributing to insulin resistance and β-cell failure[21].

High levels of glucose and fatty acids generate reactive oxygen species (ROS), which can damage cellular structures and further exacerbate insulin resistance and β-cell dysfunction[22].

The molecular mechanisms of diabetes involve complex interactions between genetic, environmental, and lifestyle factors. In Type 1 diabetes, the autoimmune destruction of β-cells leads to insulin deficiency, while in Type 2 diabetes, insulin resistance and β-cell dysfunction play central roles. Understanding these mechanisms is crucial for developing targeted therapies to manage and treat diabetes effectively.

Relationship aspects on medications

Speaking of medications that can manage both high blood pressure and diabetes, certain medications can have the effect of controlling both conditions simultaneously. However, hypertension and diabetes are separate conditions and are usually treated separately. Nevertheless, a few medications can have a positive effect on both conditions:

SGLT-2 inhibitors (Sodium-Glucose Cotransporter 2 Inhibitors): These drugs are used to treat diabetes and may have a positive effect on hypertension at the same time. SGLT-2 inhibitors lower blood sugar by inhibiting the reabsorption of glucose by the kidneys, and may lower blood pressure by increasing the excretion of sodium and water from the body. Examples include drugs such as empagliflozin and dapagliflozin[23].

SGLT2 inhibitors are not approved as blood pressure medications, but they do reduce systolic blood pressure by 4 to 6 mm Hg and diastolic blood pressure by 1 to 2 mm Hg [24]. In general, the blood pressure-lowering effects of SGLT2 inhibitors are thought to be due to a sustained reduction in plasma volume. Normally, plasma volume is highly regulated, and a decrease in plasma volume of, for example, 5% results in a rapid restoration of plasma volume due to activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, and inhibition of natriuretic peptides, which promotes reabsorption of sodium and water[25]. However, the decrease in plasma volume with SGLT2 inhibitors differs from that with conventional diuretics in that the decrease in plasma volume is less severe but is maintained [26]. This is not only due to increased natriuresis with SGLT2 inhibitors, but is also related to the fact that glucose and sodium concentrations remain high after the proximal tubule, leading the nephron to perceive that the body is in a state of high sodium and plasma volume[27]. Of course, SGLT2 inhibitors do not actually increase body sodium and plasma volume; in fact, the amount of sodium in the body decreases slightly after SGLT2 inhibitor use[28]. After SGLT2 inhibitor use, a new steady state is reached with a slightly decreased plasma volume. This blood pressure-lowering effect is also observed in patients with decreased glomerular filtration rate, which results in little or no glycemic reduction[29].

ACE inhibitors (Angiotensin-Converting Enzyme Inhibitors): Angiotensin-converting enzyme inhibitors block angiotensin-converting enzyme, which inhibits the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates aldosterone secretion, which increases sodium and water reabsorption with potassium loss. Finally it lowers blood pressure by dilating blood vessels and reducing the amount of water in the body[30].

ACE inhibitors are primarily used to treat high blood pressure, but they can also be beneficial for people with diabetes. These drugs have a nephroprotective effect, which can prevent kidney complications that can occur in people with diabetes. Common ACE inhibitors include lisinopril and enalapril[31].Angiotensin Receptor Blockers (ARBs)are used to treat high blood pressure, and may also be beneficial for people with diabetes. These drugs have a nephroprotective effect, which can help prevent kidney problems caused by diabetes. Common ARBs include losartan and valsartan[32].

CONCLUSION

Oral medication for diabetes includes metformin, sulfonylureas (e.g., glimepiride, gliclazide), SGLT2(e.g., empagliflozin, dapagliflozin) and DPP-4 inhibitors (e.g., sitagliptin, linagliptin) and for injectable medications are GLP-receptor agonists (e.g., ligrglutide, semagltide) and insulin[33].

Medication for hypertension on first-line antihypertensives are included ACE inhibitors (e.g., lisinopril, enalapril), ARBs (e.g., losartan, valsartan), Calcium Channel blockers (e.g., amlodipine, diltiazem), and Thiazide Diuretics (e.g., hydrochlorothiazide, chlorthalidone), whereas for secondary antihypertensives are beta-blockers (e.g., metoprolol, carvedilol) and aldosterone antagonists (e.g., apironolactone)[34].

There are preferred combinations to consider combination or single therapy for two cases, hypertension and diabetes.

ACE Inhibitors (e.g., Lisinopril) or ARBs (e.g., Losartan) is preferred because protect kidneys (reduce diabetic nephropathy progression) and lower blood pressure effectively with cardioprotective benefits[35].

SGLT2 Inhibitors (e.g., Empagliflozin, Dapagliflozin) are chosen because provide cardiovascular and renal benefits and lower blood glucose and reduce blood pressure. These inhibitors are recommended for patients with heart failure or chronic kidney disease[36].

Thiazide-like Diuretics (e.g., Chlorthalidone) can help control blood pressure and can be safely used alongside ACE inhibitors or ARBs. This is preferred over hydrochlorothiazide due to a longer duration of action[37].

GLP-1 Receptor Agonists (e.g., Liraglutide, Semaglutide) can be provided significant cardiovascular protection and assist in weight loss, which benefits both diabetes and hypertension[38].

Calcium Channel Blockers (e.g., Amlodipine) are chosen for additive blood pressure control when combined with ACE inhibitors or ARBs, which can be minimal interaction with glucose metabolism[39].

Medications for diabetes and hypertension are often prescribed together because the two conditions are closely linked and frequently coexist. Managing both effectively can significantly reduce the risk of complications. Here's why this combination is common: Many people with diabetes also have other components of metabolic syndrome, such as hypertension, obesity, and high cholesterol. Insulin resistance can lead to both high blood sugar (diabetes) and increased blood pressure (hypertension).

Both conditions significantly increase the risk of heart disease and stroke. Managing both together reduces this risk. Diabetes and hypertension are leading causes of chronic kidney disease. Controlling blood pressure and glucose levels helps protect kidney function.

Both conditions contribute to damage in blood vessels, leading to complications like atherosclerosis. Managing both helps mitigate this damage. Chronic inflammation is a common pathway linking diabetes and hypertension, and addressing both helps reduce systemic inflammation[40].

Some medications, such as ACE inhibitors or ARBs, are beneficial for both hypertension and diabetes as they protect the heart and kidneys while managing blood pressure. Certain antihypertensive drugs, such as calcium channel blockers and thiazide diuretics, can be safely used alongside diabetes medications.

Combination Therapy Examples are recommended as follows;

ACE Inhibitor or ARB + SGLT2 Inhibitor are excellent synergy for protecting the heart and kidneys and helps control both blood pressure and blood sugar[41].

ACE Inhibitor or ARB + Thiazide-like Diuretic + Calcium Channel Blocker are very effective multi-drug combination for resistant hypertension and maintains good glucose tolerance[42].

GLP-1 Receptor Agonist + SGLT2 Inhibitor + ACE Inhibitor/ARB are comprehensive approach for patients at high cardiovascular risk, addresses blood sugar, blood pressure, and weight simultaneously[43]. For dual benefits, the best recommended prescription are that SGLT2 inhibitors and GLP-1 receptor agonists not only lower blood sugar but also have cardiovascular and renal protective effects[44].

Prior to combination or single medication, other factors to be considered. Kidney Function should be monitored closely when using ACE inhibitors, ARBs, or SGLT2 inhibitors. Potassium levels also check the risk of hyperkalemia with ACE inhibitors/ARBs or aldosterone antagonists. Finally, it is avoided beta-blockers or high doses of diuretics that can impair glucose control.

The best combination of medications for managing hypertension and diabetes depends on individual patient factors, including the severity of both conditions, co-existing health issues, and risk factors. However, certain medications are particularly beneficial for patients with both diabetes and hypertension due to their protective effects on the cardiovascular system and kidneys.

Regardless of medication choice, lifestyle interventions (e.g., dietary changes, physical activity, smoking cessation) are critical for managing both conditions effectively.

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