

## COEXISTENCE OF HYPERTENSION WITH DIABETES MELLITUS AND ITS PHARMACOTHERAPY

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### ABSTRACT

*Diabetes mellitus and hypertension are common comorbidities, as hypertension is reported to be twice as frequent in diabetic patients as people who are non-diabetics. In diabetic condition, the risk and progression of cardiac disease, peripheral vascular disease, stroke, retinopathy, and nephropathy is greatly increased in the presence of hypertension. Persistent increase in blood pressure termed hypertension, can be either primary hypertension (essential hypertension) or secondary hypertension in nature. Primary or essential hypertension is characterized by elevated blood pressure caused by inherited factors which are characteristic of essential hypertension whereas identifiable causes such as chronic kidney diseases, endocrine disorders, constriction of the kidney arteries, or the use of drugs are among the etiology of secondary hypertension. Diabetes causes hyperinsulinemia which increases 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. Treatment of both conditions is crucial as they are considered risk factors for coronary artery disease, cerebrovascular disease, renal failure and congestive heart failure. In any age group, a considerable increase in systolic blood pressure causes a significant increase in cardiovascular disease. To achieve sufficient blood pressure control, most people with hypertension and diabetes require more than one medication. This review is aimed to discuss hypertension and diabetes mellitus comorbidities and their treatment.*

**Keywords:** Comorbidity, Diabetes; Hypertension; Drug therapy

### INTRODUCTION

Hypertension and diabetes mellitus are known to be the two most common diseases in the westernized world and the risk of both diseases increases with age. Statistically, about 2.5 to 3

million Americans have been diagnosed with both hypertension and diabetes (Bild and Teutsch, 2017). Hypertension is reported in over two-thirds of patients with diabetes

specifically type 2 diabetes (Pavlou et al., 2018).

Hypertension is prevalent among patients with diabetes. However, this depends on the duration and type of diabetes, sex, age, ethnicity and race of the patient, body mass index (BMI) of the patient, presence of other diseases such as kidney disease, history of glycemic control and many other factors. Greater body mass, longer duration of diabetes, and the presence of chronic proteinuria are all key factors of higher blood pressure, particularly systolic pressure, in the diabetic patients. Hypertension in diabetic patients is more frequent in men than in women before the fifth decade and more frequent in women thereafter. The coexistence of both diseases is more prevalent among blacks than whites; the socioeconomically disadvantaged have a higher occurrence of both conditions (Pan et al., 2016). However, other unknown factors are likely to play a role in the higher prevalence of hypertension in patients with diabetes mellitus.

The common coexistence of hypertension and diabetes is not a mere coincidence but rather due to some intertwined pathogenic mechanisms. Patients with diabetes are twice likely to develop hypertension as compared to non-diabetic patients and patients with hypertension are more likely to develop diabetes as compared to normotensive people (Wang et al., 2021).

The presence of hypertension in a diabetic patient is so fatal since it significantly increases mortality and morbidity. However, diabetes mellitus increases the risk of cardiovascular events. Hypertension is thought to be responsible for about 35-75 percent of diabetic complications (Bild and Teutsch, 2017). Long-term diabetes survivors, on the other hand, are more likely to be free of

hypertension. As a result, in industrialized nations, the coexistence of these two diseases is likely to have a significant role in overall mortality.

Despite the critical importance of the coexistence of these two diseases, much information regarding their interaction remains unclear and controversial. Nevertheless, much information of theoretical and practical relevance is available, and there are ongoing researches exploring this area.

## **MATERIALS AND METHODS**

Over 250 articles were gotten following extensive literature searches while 112 of them were adapted for this review. Excluded articles included those outside the scope of this study, or whose full texts were unavailable and not retrievable. Literature searches undertaken were carried out using search engines or databases including: Google, ResearchGate, PubMed and Elsevier. The keywords that directed our literature searches were: hypertension, diabetes, comorbidities of hypertension and diabetes, and drug treatments.

### **Main text**

#### **Hypertension**

Persistent high blood pressure (BP) also known as hypertension can be categorized according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines into (Whelton et al., 2018):

- No hypertension (BP <130/80 mmHg)
- Stage 1 hypertension (BP = 130-139/80-89 mmHg)
- Stage 2 hypertension (BP ≥140/90 mmHg)

Basically, there are two types of hypertension which are primary hypertension (essential hypertension) and secondary hypertension.

Primary or essential hypertension is characterized by elevated blood pressure caused by some lifestyle and inherited factors (Chen, 2012). Risk factors of primary hypertension include: excess dietary intake of salt, being overweight or obese, smoking, and excessive drinking (Whelton et al., 2018). Secondary hypertension (5-10% cases) are of known causes including chronic kidney disease, endocrine disorders, constriction of the kidney arteries, or birth control pills usage (Campbell et al., 2015).

Resting blood pressure persistent at or above 130/80 or 140/90 mmHg in most adults is established as high blood pressure (James et al., 2014). Between 16 and 37% of the global population is affected by high blood pressure (Oladele, 2020). Global prevalence of hypertension of people of 30-79 years of age was reported to have doubled by 50% in both women (331 million to 626 million) and men (317 million to 652 million) between the year 1990 to 2019 (NCD Risk Factor Collaboration, 2021).

### **Pathophysiology of hypertension**

Hypertension is essentially associated with increases in cardiac output and/or peripheral resistance. Mechanisms that affect cardiac output/peripheral resistance, hence, precipitating high blood pressure include genetics, sympathetic nervous system over-activity (renal mechanisms: excess sodium intake and pressure natriuresis), vascular mechanisms (endothelial cell dysfunction and the nitric oxide pathway), hormonal mechanisms (the renin-angiotensin-aldosterone system - RAAS), obesity, obstructive sleep apnea (OSA), insulin resistance and metabolic syndrome, uric acid, vitamin D, gender differences; racial, ethnic, and environmental factors, amongst others (Saxena et al., 2018).

Patients with arterial hypertension may experience an increase in cardiac output, systemic vascular resistance, or both. The cardiac output is frequently enhanced in younger patients, whereas in older patients, increased systemic vascular resistance and increased vasculature stiffness play a major impact. Increased peripheral resistance is primarily due to narrowing of both small arteries and arterioles structure in established hypertension, while a decrease in the number or density of capillaries would also play a role (Martinez-Quinones et al., 2018).

Increases in peripheral resistance in hypertension have pointed to abnormalities in the renin–angiotensin system (especially in salt and water control) and/or aberrations of the sympathetic nervous system by various studies (Franklin, 2012; DeLalio et al., 2020; Martyniak and Tomasik, 2022). Endothelial dysfunction and vascular inflammation have also been implicated (Gallo et al., 2022).

### **Etiology of hypertension**

Primary hypertension arises a result of environmental or hereditary factors, but secondary hypertension may include various etiologies, including renal, vascular, and endocrine factors (Ellis and Miyashita, 2011). Only a few minority of patients (about 2-10%) have a secondary etiology of hypertension, which accounts for 90-95 percent of adult cases (Puar et al., 2016). Insufficient drug therapy or low compliance are the most common causes of hypertensive crises (Rule et al., 2009; Krämer et al., 2019).

Secondary hypertension may be caused by any of the following:

1. **Renal causes:** About 2.5-6% of hypertension include renal parenchymal diseases and renal vascular diseases which are chronic kidney disease, polycystic

- kidney disease, renin-producing tumor and urinary tract obstruction (Preston and Epstein, 1995; Chapman et al., 2010).
2. **Vascular causes:** Vascular hypertension which usually involve the narrowing of the blood vessels of the kidneys and aorta is caused by vascular diseases such as vasculitis, aortic coarctation and collagen vascular disease (Lazea et al., 2022).
  3. **Endocrine causes:** Exogenous or endogenous hormonal abnormalities account for endocrine causes of hypertension (Sica, 2008). Endogenous hormonal causes include diseases such as Cushing's syndrome, pheochromocytoma, primary hyperaldosteronism and congenital adrenal hyperplasia (Sica, 2008). Steroid administration is an example of an exogenous cause. The use of oral contraceptives is another significant endocrine cause. Induction of hepatic angiotensinogen production with triggering of the renin-angiotensin-aldosterone system (RAAS) is the most probable mechanism of the estrogen component of oral contraceptives (Jermendy et al., 2011). Exogenous injection of various therapeutic steroids raises blood pressure (BP), primarily due to volume expansion, especially in vulnerable individuals (Barbot et al., 2019).
  4. **Neurogenic causes:** This include medical conditions such as brain tumor, autonomic dysfunction, intracranial hypertension and sleep apnea (Mann, 2018).
  5. **Drugs and toxin causes:** Some drugs and toxins that can induce hypertension include cocaine, alcohol, cyclosporine, certain decongestants containing ephedrine, erythropoietin, non-steroidal anti-inflammatory drugs (NSAIDs), tacrolimus, exposure to gas flare, herbal

medications containing licorice or ephedrine, nicotine and adrenergic medications (Grossman and Messerli, 2008; Rossi et al., 2011; Grossman et al., 2015; Ovuakporaye et al., 2019).

6. Pregnancy and hypercalcaemia also cause hypertension (Eiam-Ong et al., 2004; Kintiraki et al., 2015).

### Signs and symptoms of hypertension

Hypertension is barely accompanied by symptoms, and it is usually detected through screening or when seeking medical attention for something unrelated. Hence, it is commonly referred to as a silent killer. Headaches (especially at the posterior and usually in the morning) are common symptoms of hypertension. Other symptoms include lightheadedness, vertigo, tinnitus, distorted vision, and fainting spells (Fisher and Williams, 2019; Schmidt et al., 2020). These symptoms, on the other hand, could be due to anxiety rather than high blood pressure (Fisher and Williams, 2019).

### Diagnosis of hypertension

A systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more is considered hypertension (Al-Makki et al., 2022).

Hypertension can be diagnosed by monitoring the patient's blood pressure, conducting physical examination, conducting laboratory tests and a thorough review of the patient's medical history (Muntner et al., 2019). An ECG with 12 leads should also be acquired (Bird et al., 2020). These steps can assist the medical personnel in determining the baseline values for judging biochemical effects of therapy, presence of end-organ disease or complications, cardiovascular risk factors, as well as possible causes of hypertension (Katakam et al., 2008).

## Complications of hypertension

Hypertension is one of the main cause of premature death globally, posing a preventable risk factor for cardiovascular diseases (Mills et al., 2020). It increases the risk of cardiovascular disorders such as ischemic heart disease, heart failure, aortic aneurysms, diffuse atherosclerosis, chronic kidney disease, atrial fibrillation, cancers and pulmonary embolism, stroke, peripheral vascular disease (Mills et al., 2020). It is also a known risk factor for cognitive impairment, dementia, hypertensive retinopathy and nephropathy (Wysocki et al., 2012; Sierra, 2020).

## Pharmacological management of hypertension

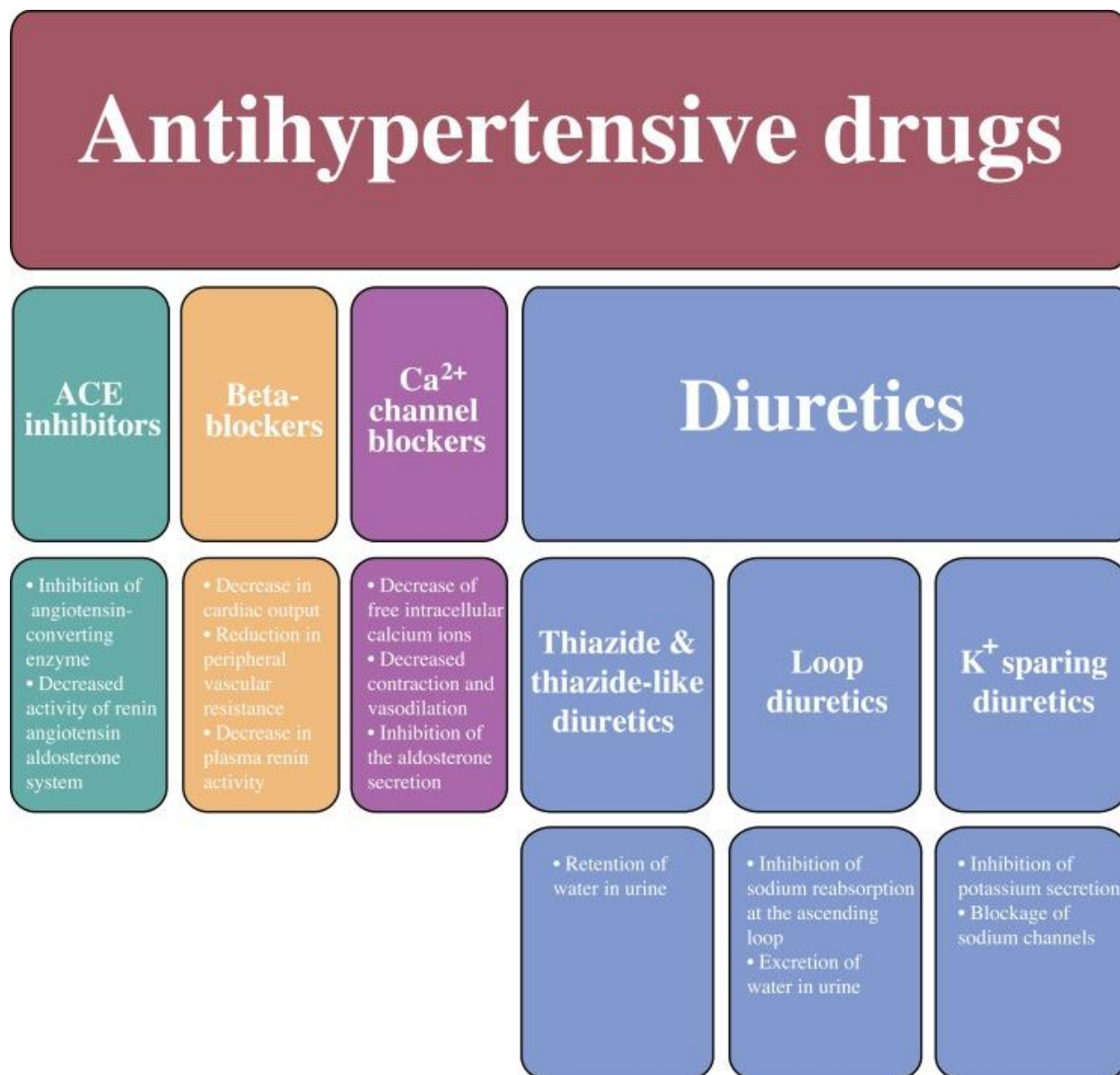
Antihypertensive agents are grouped into various categories based on their mechanism of action. The aim of these agents is to control the blood pressure and lower the risk of cardiovascular and renal complications. Their goal is also to decrease the mortality rate elicited by an increased blood -pressure. Mild or moderate hypertension can sometimes be controlled with monotherapy.

Antihypertensive agents are classified based on mechanism of blood pressure control and their respective site of action (Zisaki et al., 2015). They are majorly grouped as angiotensin converting enzyme inhibitors (e.g. lisinopril), beta-adrenergic blockers (e.g.

propranolol), diuretics (e.g. hydrochlorothiazide) and calcium channel blockers (e.g. amlodipine); others include angiotensin II receptor blockers (e.g. losartan), renin inhibitor (e.g. aliskiren), vasodilators (e.g. hydralazine), and centrally acting adrenergic drugs (e.g.  $\alpha$ -methyldopa) (**Fig 1**).

However, hypertension could be resistant (remain elevated) despite concurrent use of antihypertensive medications, resulting in suboptimal response (Acelajado et al., 2019; Moke et al., 2022). Most patients require more than one drug to achieve blood pressure control (Frohlich, 2011). The use of more than one drug is usually effective, with the selection based on minimizing or lowering the adverse effects of the combined regimen and achieving goal blood pressure (Guerrero-García and Rubio-Guerra, 2018). Combinations of medications for hypertensive patients with high cardiovascular risk have been reported by several clinical studies to be more beneficial, likewise in patients with moderate hypertension and low cardiovascular risk (Wald et al., 2009). Recommended antihypertensive combinations include (Guerrero-García and Rubio-Guerra, 2018):

- 1) Diuretics with angiotensin–renin axis inhibitors or calcium antagonists
- 2) Inhibitors of the renin–angiotensin axis with diuretics or with calcium antagonists
- 3) Beta-adrenergic blockers with dihydropyridine calcium antagonists



**Fig. 1:** Classes of antihypertensive drugs and their mechanisms of action (Zisaki et al., 2015).

### Diabetes mellitus

Diabetes mellitus (diabetes) is an endocrine disorder resulting from an irregularity in the secretion or action of insulin (Deepthi et al., 2017). It is a metabolic condition characterized by chronic hyperglycemia (ADA, 2013). Its prevalence is rapidly skyrocketing in both developing and developed countries around the world. The total number of people being diagnosed with diabetes mellitus is increasing globally with about 80% of the people with diabetes mellitus in low and middle-income countries (Lam et al., 2021). It was reported by

the International Diabetes Federation (IDF) in 2021 that globally 537 million adult people have diabetes, which is expected to rise to 643 million in 2030 and 783 by 2045 (IDF, 2021).

### Pathophysiology of diabetes mellitus

The islet of Langerhans situated in the pancreas is made up of two endocrine cells which are the insulin-secreting beta cells and the glucagon-secreting alpha cells (Wendt and Eliasson, 2022). These cells continually change their level of hormone secretion in relation to the glucose environment. An

imbalance between insulin and glucagon makes the glucose level become inappropriately distorted. In diabetes mellitus, there is either absence of insulin or there is an impaired action of insulin which results in hyperglycemia.

After a meal, there is an increase in the blood glucose level which stimulates insulin secretion. On the other hand, when in fasting conditions, the brain uses up the stored up glucose and this is independent on insulin (Röder et al., 2016. Agbonifo-Chijiokwu et al., 2023). Insulin inhibits the secretion of glucagon and lowers the concentration of serum fatty acids which causes a decline in glucose production in the liver. When there is insufficient insulin or insulin resistance, there is reduced uptake of glucose by the tissues which leads to extracellular hyperglycemia and intracellular hypoglycemia. The intracellular hypoglycemia brings about glycogenolysis and gluconeogenesis which leads to the breakdown of fats. This is responsible for diabetic ketoacidosis. It also leads to a decrease in protein synthesis and gamma globulins. Thus, causing polyphagia, cachexia and impaired wound healing. The extracellular hyperglycemia can lead to a state of hyperglycemic coma and osmotic diuresis.

### **Types of diabetes mellitus**

The main types of diabetes mellitus include type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (ADA, 2022).

Type 1 diabetes mellitus (T1DM) is one of the most common metabolic diseases found in children and it can be regarded as an autoimmune disease (Banday et al., 2020). T1DM is known as insulin-dependent diabetes mellitus (IDDM) and it is characterized by the destruction of the pancreatic beta cells

secondary to an autoimmune process which consequently results in a total destruction of pancreatic beta-cells and causes a lack of insulin secretion, leading to the metabolic abnormalities associated with T1DM (Toren et al., 2021). Although insulin deficiency is the primary defect in T1DM, there is also a defect in the administration of insulin. Deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues such as skeletal muscle (Galicía-García et al., 2020).

Type 2 diabetes mellitus (T2DM) is the more common type of diabetes and obesity is a great risk factor for developing this metabolic disease. In T2DM, there is a reduced insulin production due to pancreatic beta-cells dysfunction and impaired insulin action due to insulin resistance (Galicía-García et al., 2020). One of the characteristics of this type of diabetes is insulin resistance in peripheral tissues such as the liver and muscles with progressive failure of the beta cells of the pancreas (Galicía-García et al., 2020).

In gestational diabetes, pregnant women without previously diagnosed cases of diabetes develop consistent hyperglycemia (Plows et al., 2018). This type of diabetes may resolve immediately after delivery or may eventually precede T2DM (Kim, 2014).

### **Diagnosis of diabetes mellitus**

Early detection of people with diabetes or pre-diabetes through screening allows for early intervention, perhaps lowering future complication rates, albeit randomized trials are needed to prove benefit definitively. Diagnosis of diabetes include (ADA, 2010):

- The Haemoglobin A1C test –  $\geq 6.5\%$  is diabetes; 5.70-5.99% means prediabetes;  $< 5.7\%$  is normal

- The fasting plasma glucose (FPG) test –  $\geq 126$  mg/dl is diabetes; 100-125.99 mg/dl is prediabetes;  $< 100$  mg/dl is normal
- The oral glucose tolerance test (OGTT) (2-h plasma glucose) –  $\geq 200$  mg/dl is diabetes; 140-199.9 mg/dl is prediabetes;  $< 140$  mg/dl is normal. An abnormal OGTT result indicates that the patient's glucose tolerance is impaired (IGT).
- Random plasma glucose test with  $\geq 200$  mg/dl is diabetes

### **Signs and symptoms of diabetes mellitus**

Weight loss, polyuria (excessive urination), polydipsia (excessive thirst), and polyphagia (excessive hunger) are all hallmark symptoms of untreated diabetes. There are a number of other indications and symptoms that can indicate the start of diabetes that are not specific to the condition. These include hazy vision, headache, weariness, poor wound healing, and itchy skin. Persistent high blood glucose can cause glucose absorption in the lens of the eye, leading to changes in its shape with consequential change in vision (Wiemer et al., 2008).

### **Complications of diabetes mellitus**

Complications of diabetes mellitus may be acute or chronic. Acute complications include symptoms such as hypoglycemia, hyperglycemic crises, hyperglycemic hyperosmolar state and diabetes ketoacidosis. Chronic complications include diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, microvascular complications, and haematological abnormalities (Lim, 2014; Nentwich and Ulbig, 2015; Chawla et al., 2016; Okonofua et al., 2021; Getawa and Adane, 2022; Okonofua et al., 2023).

Majority of the forms of diabetes increase the risk of long-term complications. These complications usually develop after many

years but may be the first symptom in those who have been undiagnosed as at that time. The major long-term complications of diabetes mellitus is related to damage of the blood vessels. Diabetes mellitus doubles the risk of cardiovascular diseases and about 75% of deaths in people with diabetes mellitus are as a result of coronary artery disease. Other macrovascular diseases linked with diabetes mellitus include stroke, and peripheral artery disease (Papatheodorou et al, 2018).

### **Pharmacological management of diabetes mellitus**

T1DM has no known cure and is life-long. Insulin is the best choice for the management of T1DM and can be administered as insulin pumps or injections (McCall and Farhy, 2013). Insulins may be short or rapid acting, intermediate acting or long acting. A process known as islet grafting has been explored as a therapy for T1DM in selected patients with inappropriate glucose control despite insulin therapy. Artificial pancreas is a closed loop insulin delivery (Templer, 2022). It is associated with a continuous monitor of glucose to insulin pump delivering correct amount of insulin automatically when the monitor specify the need for the pump (Templer, 2022).

Drugs useful in the treatment of T2DM include oral hypoglycemic agents such as sulphonylureas, thiazolidinediones, glucosidase inhibitors and biguanides (Padhi et al., 2020). These drugs work to correct metabolic disorder such as insulin resistivity or insufficient production of insulin. They are administered with a healthy diet plan and appropriate changes in lifestyle. The sulphonylureas include glimepride, gliplizide and glyburide, biguanide include metformin, thiazolidinedione include the proglitazone and



the alpha glucosidase inhibitors include acarbose.

In the treatment of T2DM, metformin has been applied for more than half a century (Zhou et al., 2018). It has a lot of advantages as compared to other classes of drugs as it does not promote weight gain and it has cardio-protective effect (Driver et al., 2018; Loi et al., 2019). Guidelines from the American Diabetes Association (ADA), the European Association for Study of Diabetes (EASD) and the American College of Endocrinology (ACE) recommend early initiation of metformin as the first line agent in the treatment of type 2 diabetes (Deepthi et al., 2017).

Current class of drugs newly developed in treating diabetes includes glucagon-like peptides-1 (GLP-1) mimetics, sodium-glucose transporter protein-2 (SGLT-2) inhibitors, amylin mimetics, dipeptidyl peptidase-4 (DPP-4) inhibitors and dual peroxisome proliferator-activated receptor (dual PPAR) agonist (Deepthi et al., 2017). GLP-1 mimetics or agonists are glucagon-like peptides are given by injection to regulate glucose level. Their action causes glucose dependent secretion of insulin. GLP-1 promotes weight reduction and are powerful in increasing glycemic control (Bossart et al., 2022). Sodium-glucose transporter protein-2 (SGLT-2) inhibitors helps to lower the kidney glucose level and causes large excretion of glucose via the urine (Tang et al., 2022). Amylin agonists are administered before food and they inhibit the release of glucagon while eating and slows down the action of food emptying from the stomach (Boyle et al., 2022). DPP-4 inhibitors (gliptins) acts by an enzyme which destroys incretin which is a gastrointestinal hormone (Yazbeck et al., 2021). This class of drug is usually prescribed to type 2 diabetic patients

who are non-responsive to metformin and sulphonylureas. Dual PPAR agonist is potent in achieving glucose homeostasis (Quaoud et al., 2022).

Medicinal plants have also been reported to be effective in the management of diabetic state (Asiwe et al., 2023; Moke et al., 2023a).

### **Hypertension in diabetic patients**

Diabetes mellitus and hypertension are two common comorbid chronic conditions that predispose patients to cardiovascular diseases (Petrie et al., 2018). Hypertension is twice as frequent in diabetics as compared with non-diabetic patients (Petrie et al., 2018). Hypertension is a serious condition that it becomes more severe if accompanied with diabetes as a comorbidity. These impacts include the following in the case of diabetes and hypertension:

- a) Increased fluid volume – diabetes increases the total amount of fluid in the body, which tends to raise blood pressure (Han et al., 2020).
- b) Increased arterial stiffness – diabetes can decrease the ability of the blood vessels to stretch, increasing average blood pressure (Gordin and Groop, 2016).
- c) Impaired insulin handling – changes in the way the body manufactures and processes insulin can cause blood pressure to rise immediately (Zhou et al., 2012; Petersen and Shulman, 2018).

Apart from these factors, both diseases are likely to occur together simply because they have a common set of risk factors (Petrie et al., 2018).

### **The link between diabetes and hypertension**

Diabetes causes hyperinsulinemia which upturns 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 (Geleijnse et al., 2014; Mancusi et al., 2020).

Diabetes mellitus may be characterized by insulin resistance and there exist a link between insulin resistance and hypertension. According to clinical research, roughly half of hypertensive people have hyperinsulinemia or glucose intolerance, whereas up to 80% of people with type 2 diabetes have hypertension (Zhou et al., 2012). Insulin, in addition to its metabolic actions, causes vasorelaxation by boosting the synthesis of nitric oxide (NO) in endothelium and regulates salt homeostasis by increasing sodium reabsorption in the kidney, all of which contribute to blood pressure management. Insulin resistance can develop not only in the conventional insulin-responsive tissues, but also in cardiovascular tissues, where insulin plays a role in the development of cardiovascular illnesses and hypertension, according to recent research (Schulman and Zhou, 2009). Insulin resistance is frequently linked to the metabolic syndrome and hypertension, all of which are linked to an increased risk of type 2 diabetes and cardiovascular disease (Mancusi et al., 2020).

Insulin causes a net response in sympathetic outflow in healthy people while also blunting the vasoconstrictive effect of this sympathetic activation (Lembo et al., 2010; Thorp and Schlaich, 2015). Insulin, on the other hand, causes three times higher sympathetic activation in hypertension patients than in healthy people, and its vaso-relaxant effect is also diminished (Lembo et al., 2010). This process is implicated in peripheral vascular resistance dysregulation, which contributes to elevated blood pressure levels. Furthermore, anomalies in insulin's counter-regulatory

activities play a role in the development of hypertension-related disease, as does insulin resistance and the resulting hyperinsulinemia. Impairment of cell membrane ion exchange, increased sympathetic nervous and renin-angiotensin systems, decreased atrial natriuretic peptide activity, sodium retention, and plasma volume expansion all contribute to chronic kidney disease development (Lembo et al., 2010).

Insulin resistance is frequently caused by obesity. Both hypertension and diabetes are linked to obesity, posing a considerable burden in terms of patient morbidity and death, as well as rising health-care costs (Wondmkun, 2020).

Another relationship between insulin resistance and hypertension could be salt sensitivity (Yatabe et al., 2010; Ertuglu et al., 2021). In hypertensive patients with salt sensitivity, but not in those with salt resistance, a high salt diet reduces insulin sensitivity (Lastra et al., 2010). Salt sensitive hypertension is more seen in groups of individuals who are obese, elderly, postmenopausal, and/or have the metabolic syndrome. Diabetes and cardiovascular diseases are more common in these populations.

### **Management of hypertension in diabetic patients**

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 diseases (Hansson et al., 2018).

### **Drug therapy**

Drug therapy is an important step for most patients during treatment. Numerous researches 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 (Rizvi, 2017; Liu et al., 2023; Moke et al., 2023b). Findings from various research has shown that the following drugs are good for treatment of hypertension in diabetic patients:

### ***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 (Zhang et al., 2020). ACE inhibitor therapy results in 20 to 30 percent decrease in the risk of stroke, coronary heart disease, and major cardiovascular events (Braunwald et al., 2004). ACE inhibitors are found to be more beneficial when compared with other antihypertensives in the reduction of acute myocardial infarction, cardiovascular events, and mortality (van Vark et al., 2012). Captopril and atenolol are similar in terms of reduction in microvascular and macrovascular complications.

### ***Diuretics***

Patients with diabetes and systolic hypertension have been proven to benefit from thiazide diuretics (Rizvi, 2017). In older non-insulin-treated diabetic individuals with isolated systolic hypertension, chlorthalidone medication is useful in averting significant cerebrovascular and cardiovascular events. Lower thiazide doses (e.g., hydrochlorothiazide) are generally well tolerated and do not cause metabolic side effects. In patients with renal impairment, thiazide diuretics are less effective, hence loop diuretics are chosen (Shah et al., 2017).

### ***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. 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 (Pugh et al., 2019).

### ***Angiotensin II Receptor Blockers (ARB)***

Candesartan and lisinopril are used to treat patients with type 2 diabetes, hypertension, and microalbuminuria. Candesartan is as effective as lisinopril in blood pressure reduction and minimization of microalbuminuria. Losartan therapy produced a renoprotective effect independent of its blood-pressure-lowering effect in patients with type 2 diabetes and nephropathy. The efficacy of losartan in the management of hypertensive diabetic comorbidity has been reported (Moke et al., 2023c). 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 (Sachpekidis et al., 2019).

### ***Beta Blockers***

The use of beta blockers in diabetic patients has traditionally been discouraged due to negative metabolic consequences and the masking of hypoglycemia symptoms (Dungan et al., 2019). There was no difference in hypoglycemia episodes between patients treated with atenolol and those treated with captopril, although the atenolol group gained

more weight. Cardio-selective beta blockers are recommended over non-selective beta blockers since they are linked to reduced hypoglycemia consciousness and lower cholesterol and glucose levels. When compared to typical beta blockers, the alpha beta blocker carvedilol causes lower changes in lipid and glucose levels. Because of its demonstrated capacity to reduce cardiovascular morbidity and mortality in those with atherosclerotic heart disease, beta blocker medication may be beneficial in many diabetic individuals (Du et al., 2014).

### **Renin Inhibitors**

With the development of the first direct renin inhibitor, aliskiren, recently approved by the US Food and Drug Administration (FDA) for the treatment of hypertension in diabetic patients, a new and promising strategy in renin-angiotensin aldosterone system blockage has begun. Aliskiren is generally well tolerated, and unlike ACE inhibitors, it does not cause substance P or bradykinin buildup. As a result, side symptoms like cough and angioedema are quite infrequent. It has a good safety and tolerability record, whether used alone or in combination with other medications. In multiple placebo-controlled clinical trials, aliskiren monotherapy showed significant, dose-dependent antihypertensive effects (Gerc et al., 2009; Zhao et al., 2020).

### **CONCLUSION**

Hypertension and diabetes are two critical comorbidities that may lead to mortality if not handled properly. Diabetes cause hyperinsulinism, a potential trigger of hypertension, thus, a divorce between these two conditions may not be possible. The resultant effect of hyperinsulinemia and insulin resistance on diabetic patients is the development of hypertension due to its direct action on sodium and water retention as well

as its direct action on blood vessel reactivity. Therefore, diabetic patients should have their blood pressure monitored constantly and should maintain healthy lifestyle. Diabetic patients with hypertension should take appropriate antihypertensives, and combination therapy should be administered to hypertensive diabetic patients to attain blood pressure control in order to prevent mortality and lower the risk of other comorbidities.

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