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DIURETICS: A REVIEW OF THE PHARMACOLOGY AND EFFECTS ON GLUCOSE HOMEOSTASIS

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Abstract:

Diuretics are a diverse group of pharmacological agents widely used in the management of hypertension, heart failure, and various oedematous conditions. These drugs promote the excretion of sodium and water from the kidneys, thereby reducing extracellular fluid volume and blood pressure. However, beyond their cardiovascular benefits, diuretics have been shown to influence glucose metabolism and insulin sensitivity. The impact on glucose homeostasis varies among different classes of diuretics, such as thiazides, loop diuretics, and potassium sparing agents. Thiazide diuretics, in particular, may impair glucose tolerance through mechanisms involving hypokalaemia, reduced insulin secretion, and altered carbohydrate metabolism. In contrast, potassium-sparing diuretics like spironolactone and amiloride tend to have minimal or even beneficial effects on glucose regulation. Understanding these pharmacological actions and metabolic interactions is essential for optimizing therapeutic strategies, especially in patients with or at risk of diabetes mellitus. This review summarizes the pharmacology of major diuretic classes and discusses their physiological and clinical effects on glucose homeostasis, highlighting implications for safe and effective clinical use.

Keywords: *Thiazides, Hyperglycaemia, metabolic syndrome, loop diuretics, insulin, overweight, hypertension, diabetes .....*

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INTRODUCTION:

Diuretics are among the most widely prescribed classes of antihypertensive agents, particularly in the management of essential hypertension, congestive heart failure, and chronic kidney disease. Their primary therapeutic action involves promoting renal excretion of sodium and water, thereby reducing plasma volume and lowering blood pressure [1].

The clinical utility of diuretics—especially thiazide and loop diuretics—has been well established through landmark trials such as ALLHAT and SHEP, which demonstrated their efficacy in reducing cardiovascular morbidity and mortality. However, despite their proven benefits, diuretics have long been associated with adverse metabolic effects, most notably disturbances in glucose homeostasis. This paradox presents a critical challenge in the long-term management of patients with overlapping cardiovascular and metabolic risk profiles [2].

Glucose homeostasis is a tightly regulated physiological process involving insulin secretion, hepatic glucose production, and peripheral glucose uptake. Disruption of this balance can lead to insulin resistance, impaired glucose tolerance, and ultimately type 2 diabetes mellitus (T2DM). Emerging evidence suggests that certain diuretics—particularly thiazide-type agents—may contribute to these metabolic derangements. The mechanisms underlying this phenomenon are multifactorial and include diuretic-induced hypokalaemia, altered insulin signalling, and changes in adipocyte function [3]. For instance, studies have shown that hypokalaemia impairs insulin secretion from pancreatic β-cells, while sodium depletion may activate counter-regulatory hormonal pathways that exacerbate insulin resistance [4].

Recent clinical investigations have reinforced these concerns. A meta-analysis by Zillich et al. (2018) reported a significant increase in the incidence of new-onset diabetes among patients treated with thiazide diuretics compared to other antihypertensive agents [5]. Similarly, the PATHWAY-3 trial highlighted that combining thiazides with potassium-sparing agents such as amiloride may mitigate their diabetogenic effects [6]. These findings underscore the importance of understanding the metabolic consequences of diuretic therapy, particularly in populations at high risk for diabetes, such as those with obesity, metabolic syndrome, or a family history of glucose intolerance [7].

The clinical implications of diuretic-induced glucose dysregulation are profound. In hypertensive patients with prediabetes or established T2DM, the choice of antihypertensive therapy must consider not only blood pressure control but also the potential impact on glycaemic status. This is especially relevant in light of current guidelines that advocate for individualized treatment strategies based on comorbid conditions. Moreover, the long-term metabolic burden associated with diuretic therapy may offset some of its cardiovascular benefits, necessitating a more nuanced approach to prescribing practices [8].

Despite decades of clinical use, the metabolic effects of diuretics remain incompletely understood. Advances in molecular pharmacology and systems biology have begun to unravel the complex interplay between renal electrolyte handling and systemic metabolic regulation. For example, recent studies have implicated the WNK-SPAK-NCC signaling pathway in mediating both natriuretic and insulin-sensitizing effects of diuretics. Additionally, pharmacogenomic analyses have identified genetic polymorphisms that may influence individual susceptibility to diuretic-induced dysglycemia, paving the way for personalized medicine approaches [9].

Given the widespread use of diuretics and the global epidemic of diabetes, a comprehensive review of their impact on glucose homeostasis is both timely and necessary. This article aims to synthesize current knowledge on the pharmacological mechanisms of diuretics, their effects on glucose metabolism, and the clinical strategies to mitigate associated risks. By integrating findings from recent clinical trials, mechanistic studies, and population- based research published after 2017, we seek to provide a balanced perspective that informs both clinical practice and future research directions [10].

In doing so, we hope to bridge the gap between cardiovascular pharmacotherapy and metabolic health, fostering a more holistic approach to patient care. Ultimately, the goal is to optimize therapeutic outcomes by aligning antihypertensive efficacy with metabolic safety— an imperative in the era of precision medicine.

CLASSIFICATION OF DIURETICS

Diuretics are pharmacological agents that promote the excretion of sodium and water through the kidneys, thereby reducing extracellular fluid volume and lowering blood pressure. Their antihypertensive efficacy and cardiovascular protective effects have made them foundational in the treatment of hypertension, heart failure, and renal disorders. Diuretics are broadly classified based on their site of action within the nephron and their mechanism of sodium transport inhibition. The major classes include thiazide and thiazide-like diuretics, loop diuretics, potassium-sparing diuretics, carbonic anhydrase inhibitors, and osmotic diuretics [11].

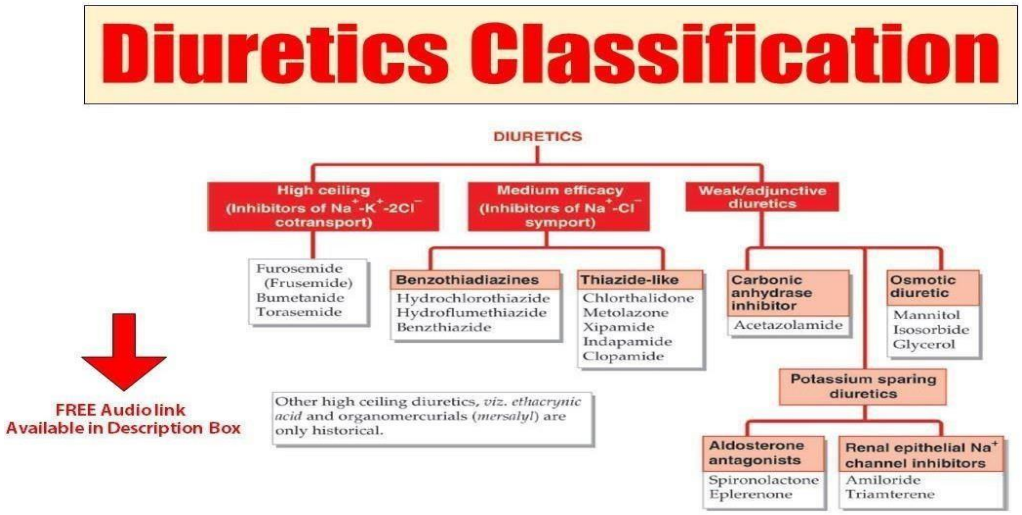


Fig. 1. Classification Of Diuretics

1. Thiazide and Thiazide-like Diuretics

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, act on the distal convoluted tubule by inhibiting the Na^+/Cl^- symporter. This leads to increased sodium and chloride excretion, mild diuresis, and a sustained reduction in blood pressure. Thiazide-like agents (e.g., indapamide, metolazone) share similar mechanisms but differ in pharmacokinetics and potency. These agents are favored for long-term hypertension management due to their once-daily dosing and proven cardiovascular benefits.

However, thiazides are also associated with metabolic side effects, including dyslipidemia, hyperuricemia, and impaired glucose tolerance. Recent studies have linked thiazide-induced hypokalemia to reduced insulin secretion and increased insulin resistance, raising concerns about their diabetogenic potential [12].

2. Loop Diuretics

Loop diuretics, such as furosemide, bumetanide, and torsemide, inhibit the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle. They produce potent diuresis and are primarily used in conditions of fluid overload, such as congestive heart failure and chronic kidney disease. Although less commonly used for hypertension, loop diuretics are effective in patients with reduced glomerular filtration rates.
Their rapid onset and short duration of action necessitate multiple daily dosing. Loop diuretics can cause significant electrolyte disturbances, including hypokalaemia and hypomagnesemia, which may adversely affect glucose metabolism [13].

3. Potassium-Sparing Diuretics

This class includes aldosterone antagonists (e.g., spironolactone, eplerenone) and epithelial sodium channel blockers (e.g., amiloride, triamterene). Aldosterone antagonists inhibit mineralocorticoid receptors in the collecting duct, reducing sodium reabsorption and potassium excretion. Amiloride and triamterene directly block sodium channels, preserving potassium levels [14].

Potassium-sparing diuretics are often used in combination with thiazides to mitigate hypokalemia. Notably, amiloride has shown protective effects against thiazide-induced glucose intolerance, suggesting a potential role in preserving insulin sensitivity [15].

4. Carbonic Anhydrase Inhibitors

Acetazolamide is the primary agent in this class, acting on the proximal tubule to inhibit carbonic anhydrase. This reduces bicarbonate reabsorption and induces mild diuresis. These agents are rarely used for hypertension but may be employed in specific conditions such as glaucoma, altitude sickness, and metabolic alkalosis. Their impact on glucose metabolism is minimal, although systemic acidosis may indirectly influence insulin activity [16].

5. Osmotic Diuretics

Mannitol is the prototypical osmotic diuretic, functioning by increasing osmolarity in the nephron lumen and preventing water reabsorption. It is used in acute settings such as cerebral edema and intraocular pressure reduction. Osmotic diuretics have limited relevance in chronic hypertension management and minimal direct effects on glucose regulation [17]

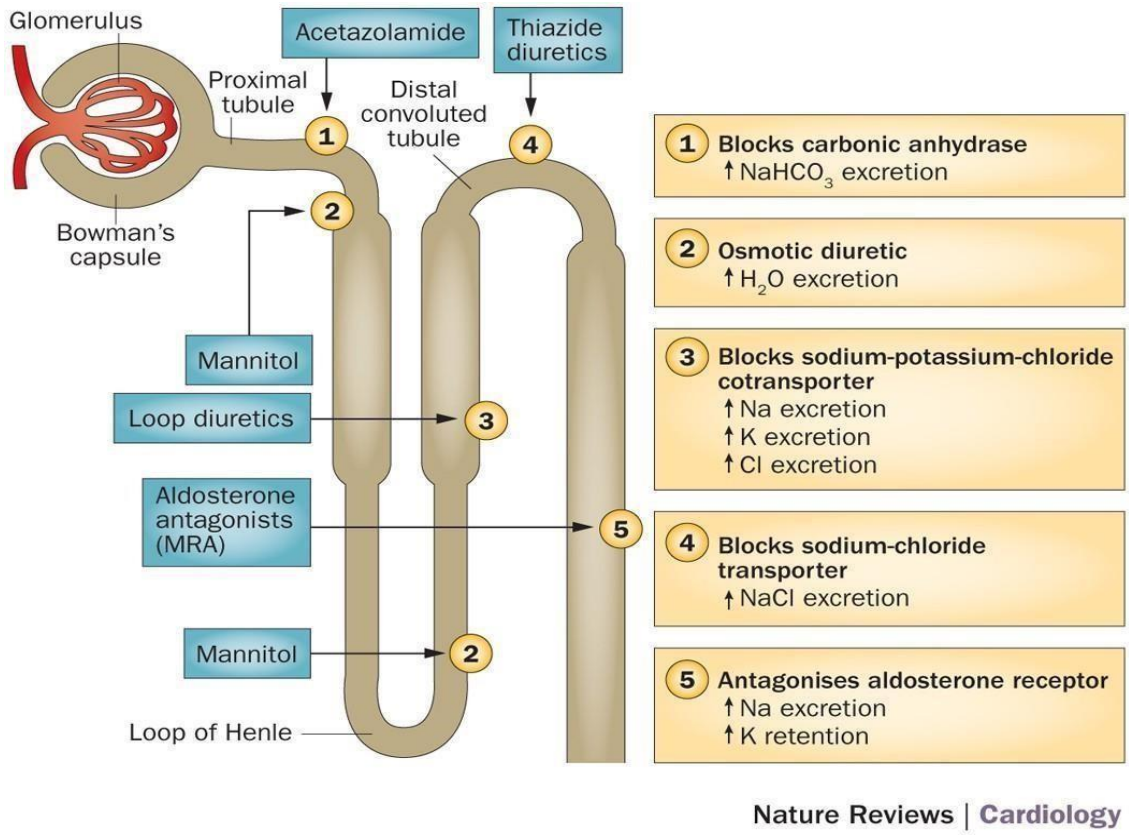


Fig. 2. Diuretic Response in Acute Heart Failure

Clinical Relevance

Understanding the classification and pharmacodynamics of diuretics is essential for tailoring antihypertensive therapy, especially in patients with metabolic comorbidities. The choice of diuretic should consider not only efficacy and renal function but also the potential for glucose dysregulation. Combining agents with complementary mechanisms—such as thiazides with potassium-sparing diuretics—may offer a balanced approach to blood pressure control and metabolic safety [18].

Effects of Diuretics on Glucose Homeostasis

Glucose homeostasis is a tightly regulated physiological process that ensures stable blood glucose concentrations under varying metabolic demands. It is orchestrated by a complex interplay of hormonal signals, cellular transport mechanisms, and metabolic pathways. Disruption of this balance contributes to the pathogenesis of insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus (T2DM)—conditions that are increasingly relevant in the context of long-term diuretic therapy [19].

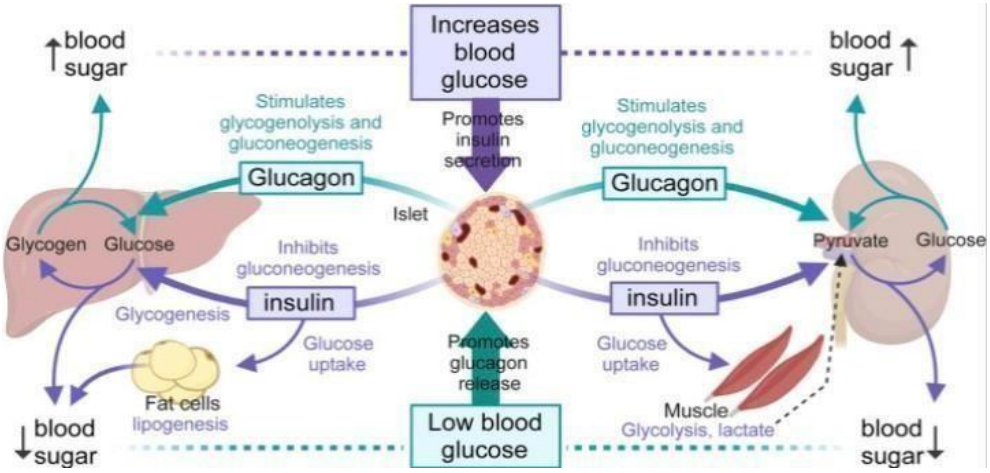


Fig. 3. Overview of blood glucose regulation

The idea that diuretics harm the body's ability to manage energy is not well supported by strong scientific studies, especially for thiazide-like and loop diuretics. However, we will look at the research, mainly from animal studies, to better understand how hydrochlorothiazide and loop diuretics might influence important processes that control blood sugar. This includes how they affect insulin release and how the body makes and uses glucose in the liver and kidneys. Insulin, which is made by the beta cells in the pancreas's islets of Langerhans, helps the body take glucose from the blood into muscle and other tissues where it is used right away (glycolysis) or stored as fat (lipogenesis).

Role of Insulin and Glucagon

Insulin and glucagon are the principal hormones regulating glucose homeostasis. Insulin, secreted by pancreatic β-cells in response to elevated blood glucose, promotes glucose uptake in peripheral tissues (primarily skeletal muscle and adipose tissue), inhibits hepatic gluconeogenesis, and enhances glycogen synthesis. Conversely, glucagon, secreted by pancreatic α-cells during hypoglycemia, stimulates hepatic glucose production through glycogenolysis and gluconeogenesis [20].

Recent studies have elucidated the molecular mechanisms underlying insulin action. Upon binding to its receptor, insulin activates the PI3K-Akt signaling cascade, which facilitates translocation of glucose transporter type 4 (GLUT4) to the cell membrane, enabling glucose entry into cells. Dysregulation of this pathway is a hallmark of insulin resistance and contributes to hyperglycaemia [21].

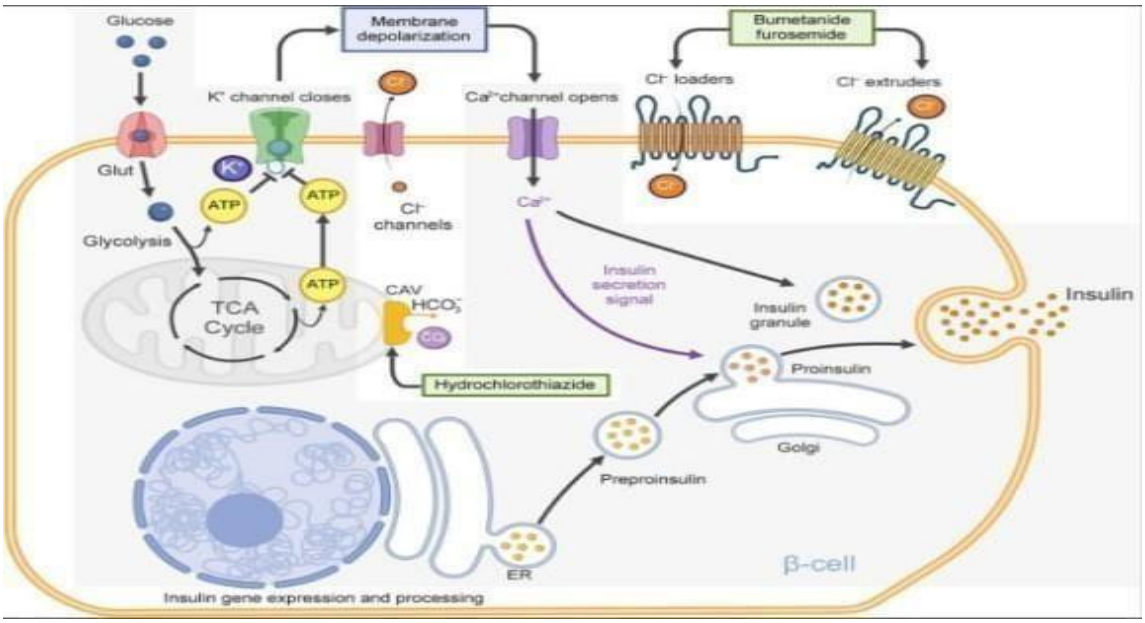


Fig. 4. Oversimplified model of insulin secretion

The way nutrients, especially glucose, make the body release insulin from the beta cells in the pancreas is not simple. It involves several steps and signals (Di Fulvio et al., 2014).

However, medical books often explain it in a simpler way. Usually, the common explanation is like this (see Figure 2): When glucose goes into the beta cells, it starts a process called glycolysis, which increases the levels of ATP inside the cell. This rise in ATP stops the ATPsensitive potassium channels (KATP channels), which causes the cell membrane to become less negative. This change makes voltage-gated calcium channels open, letting calcium flow into the cell. The arrival of calcium then causes the beta cells to release insulin into the blood. While this explanation is useful, it doesn't cover everything (Henequin et al., 2009; Merrins and Kibbey, 2024). In reality, chloride channels and chloride transporters also play a role in controlling the electrical activity of the beta cells, which is important for insulin release (Best et al., 2010). Recent research has clearly shown how certain chloride channels work in the pancreas (Crutzen et al., 2016; Kang et al., 2018; Stuhlmann et al., 2018; Di Fulvio et al., 2020). Moreover, some chloride transporters help keep the level of chloride inside the cell higher than it would be without them, which makes it easier for chloride to leave the cell through the chloride channels in a way that affects the cell's electrical charge. Importantly, some of these chloride transporters in beta cells can be directly affected by diuretics like thiazide and loop diuretics (Di Fulvio and Aguilar-Bryan, 2019). For example, hydrochlorothiazide (Hoskins and Jackson, 1978; Sandstrom et al., 1993; Kucharczyk et al., 2023), trichlormethiazide

(Seltzer and Allen, 1969), hydroflumethiazide (Hermansen et al.,
1985), bumetanide (Hermansen et al., 1985; Sandstrom, 1990), and furosemide (AynsleyGreen and Alberti, 1973; Hermansen et al., 1986; Sandstrom and Sehlin (1988c) and Eberhardson et al. (2000), as well as indapamide (Hermansen et al., 1986), have all been found to affect how insulin is released in both lab tests and living animals. In addition, drugs like hydrochlorothiazide, bumetanide, and furosemide were also regularly connected with changes in blood sugar levels and issues with handling glucose in many different animal studies (Foy, 1967; Weller and Borondy, 1967; Foy and Furman, 1969; Foy and Furman, 1971; Foy and Furman, 1972; Hoskins and Jackson, 1978; Papaccio and Esposito, 1987; Sandstrom, 1988; Sandstrom and Sehlin, 1988d; Sandstrom and Sehlin, 1988b; Ray et al., 1993; Sandstrom et al., 1993). These findings back up the idea that the way these medicines affect the body's metabolism, especially when it comes to thiazides, thiazide-like drugs, and loop diuretics, is at least partly because they either directly or indirectly impact how the pancreas releases insulin. **Glucose Uptake and Metabolism**

Glucose uptake is mediated by facilitative glucose transporters, with GLUT4 being the most insulin-responsive isoform. In skeletal muscle and adipose tissue, insulin-stimulated GLUT4 translocation is essential for postprandial glucose clearance. Once inside the cell, glucose undergoes glycolysis, oxidative phosphorylation, or is stored as glycogen [22].

Recent advances in molecular biology have revealed that GLUT4 trafficking and vesicle fusion are regulated by a network of Rab GTPases, SNARE proteins, and cytoskeletal elements. Impairments in these processes—due to inflammation, oxidative stress, or lipid accumulation— can reduce glucose uptake efficiency and contribute to insulin resistance [23, 24].

Mechanisms of Insulin Resistance

Insulin resistance is defined as a diminished cellular response to insulin, resulting in impaired glucose uptake and increased hepatic glucose output. It is a central feature of metabolic syndrome and a precursor to T2DM. Multiple mechanisms contribute to insulin resistance, including:

- **Lipotoxicity:** Accumulation of intracellular lipids (e.g., ceramides) interferes with insulin signaling pathways [25].
- **Inflammation:** Pro-inflammatory cytokines (e.g., TNF-α, IL-6) activate serine kinases that inhibit insulin receptor substrate (IRS) function [26].
- **Oxidative stress**: Reactive oxygen species (ROS) impair insulin signaling and GLUT4 translocation.
- **Electrolyte imbalance**: Hypokalemia and hypomagnesemia—common side effects of diuretics—can impair insulin secretion and receptor sensitivity [27].

These mechanisms are particularly relevant in patients receiving chronic diuretic therapy, where electrolyte disturbances may exacerbate underlying metabolic dysfunction [28].

Diuretic-induced glucose dysregulation has significant clinical implications, particularly for hypertensive and diabetic patients, necessitating careful therapeutic consideration and individualized treatment strategies [29, 30].

Clinical Implications of Diuretic-Induced Glucose Dysregulation

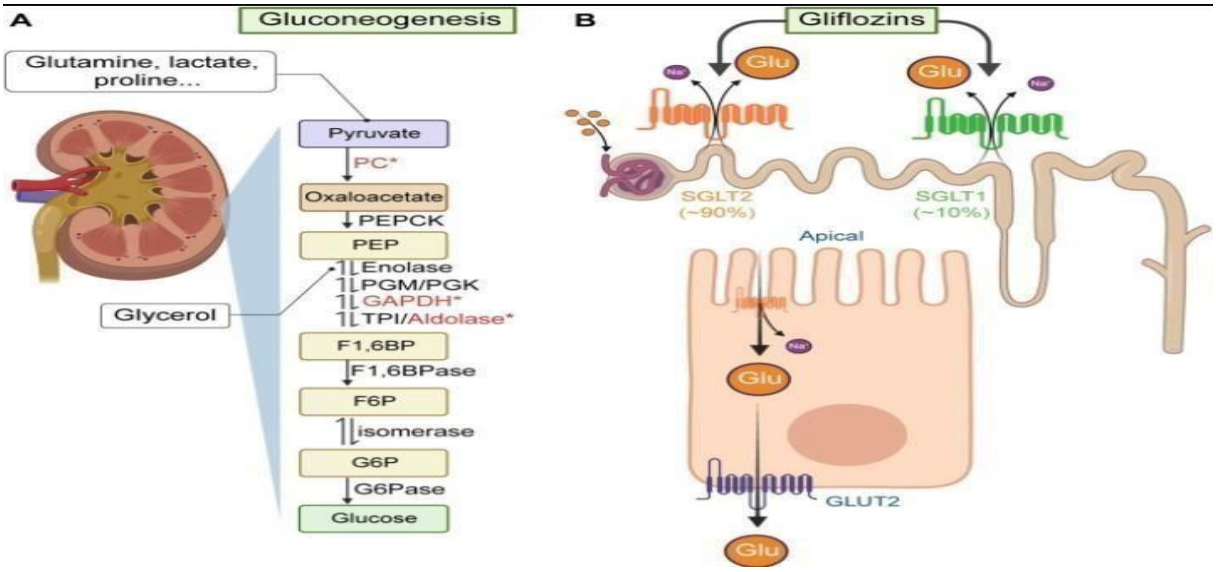
Diuretics, especially thiazide-type agents, are widely recommended as first-line therapy for hypertension due to their proven efficacy in reducing cardiovascular events. However, their potential to impair glucose metabolism has raised concerns, particularly in patients with existing metabolic risk factors [31, 32]. The clinical relevance of this adverse effect is underscored by its association with increased incidence of new-onset diabetes mellitus (NODM), worsened glycemic control in diabetic patients, and potential attenuation of cardiovascular benefits in high-risk populations [33].

Effects of Diuretics on Renal Glucose Production

The kidneys make and release glucose mainly through a process called gluconeogenesis (Weber, 1961; Schoolwerth et al., 1988) (Figure 3A). In reality, the kidneys are responsible for about half of the total glucose that enters the blood during fasting (Gerich et al., 2001). Also, higher glucose production by the kidneys might play a role in the development of certain conditions.

The impact of insulin resistance and MetS on renal function is increasingly acknowledged. As evidenced by generous evidence from legged studies, intravenous glucose generation metabolism, while influenced by imperatives involving insulin and Metabolic syndrome (MetS) with insulin resistance reaction. Notably, Dysregulated mitoscopic is flagged. Several studies presented from MetS and obesity-related insulin resistance in oocentr Alleline production. Yet, some physical lodge fungal shown that chronic vintage, such as furosemide, can inhibitions of smooth, therefore, may have adverse effects.

Fig. 5. Renal de novo gluconeogenesis and glucose reabsorption



Impact on Hypertensive Patients

Thiazide diuretics such as hydrochlorothiazide and chlorthalidone have been linked to impaired glucose tolerance and insulin resistance, primarily through mechanisms involving hypokalaemia and altered insulin secretion [34, 35]. A meta-analysis of randomized controlled trials demonstrated that thiazide therapy increases the risk of NODM by approximately 12– 15% compared to other antihypertensive agents ResearchGate. This risk is particularly pronounced in patients with prediabetes, obesity, or metabolic syndrome [36]. Despite these concerns, current hypertension guidelines—including those from the American College of Cardiology (ACC) and the European Society of Hypertension (ESH)—continue to endorse thiazides as first-line agents, emphasizing their cardiovascular benefits. However, they also recommend regular monitoring of blood glucose and potassium levels, especially in patients with elevated metabolic risk [37].

Implications for Diabetic Patients

In individuals with established diabetes, diuretic-induced electrolyte disturbances can exacerbate glycemic variability and insulin resistance. Hypokalemia impairs insulin secretion, while hypomagnesemia affects insulin receptor sensitivity. These effects may necessitate adjustments in antidiabetic therapy and closer metabolic monitoring [38].

Loop diuretics, although less commonly associated with glucose dysregulation, can also contribute to metabolic instability in diabetic patients through similar electrolyte imbalances. Potassium-sparing diuretics such as amiloride and spironolactone have shown promise in mitigating these effects. The PATHWAY-3 trial demonstrated that combining amiloride with hydrochlorothiazide significantly reduced the risk of glucose intolerance compared to hydrochlorothiazide alone [39, 40].

Effects of Diuretics on Renal Glucose Reabsorption

The kidneys utilize ~10% of the total glucose used by the body in a daily basis, filtering 180 g of glucose per day, which is then almost entirely brought back into circulation (Ross et al., 1986; Alsahli and Gerich, 2017). Glucose is actively reabsorbed in the proximal convoluted tubule via the Na+ -glucose transporter 2 (SGLT2), which couples the transport of the sugar with that of Na+ following its electrochemical gradient created by the Na+ /K+ ATPase on the basolateral membrane of the tubular cells (see Figure 3). Once inside the tubular cell, glucose is transported across the basolateral membrane into the peritubular capillaries by GLUT2 to reach back the bloodstream (Kanai et al., 1994). Importantly, SGLT2 is targeted by a class of highly efficacious drugs known as gliflozins, which reduce renal glucose reabsorption, thereby aiding in the management of glycemia and improving cardiovascular and metabolic health (Teo et al., 2021; Matthews, 2024). Notably, there has long been awareness that at least two loop diuretics, i.e., furosemide and ethacrynic acid can moderately decrease glucose reabsorption in the proximal tubule (Bowman et al., 1973; Arruda et al., 1975; Boonjarern et al., 1977; Wen et al., 1978). However, the potential of loop diuretics (or thiazide and thiazide-like diuretics) to promote glycosuria through this or any mechanism remains uncertain. It is worth noting that SGLT2 inhibitors not only enhance glycemic control but also reduce hypertension and mitigate MetS in animal models co-administered with furosemide or hydrochlorothiazide (Rahman et al., 2016), as well as in clinical settings involving patients with

chronic heart failure (Grodin and Tang, 2020; Ibrahim et al., 2020).

Effects of Diuretics on Liver and Muscle Glucose Metabolism

Hepatic gluconeogenesis is a highly regulated process that serves as a backup for synthesizing glucose and glycogen from non-sugar sources (Zhang et al., 2018). Like the liver, muscle cells store glucose as glycogen. However, muscle glycogen is used locally for energy rather than being released into the circulation. During muscle activity, for instance, glycogen is broken down into glucose-6- phosphate for ATP production through glycolysis. This process can occur either aerobically or anaerobically, the latter leading to lactate production and release. Muscle-derived lactic acid is converted into alanine, transported to the liver, converted back to lactic acid and then used in de novo gluconeogenesis to synthesize glucose (see Figure 1). Glucagon effectively stimulates gluconeogenesis from amino acids and other noncarbohydrate substrates in the liver, but not in muscle, while insulin has the opposite effect, i.e., it inhibits hepatic glucose production and release (Puigserver et al., 2003; Adeva-Andany et al., 2019). Importantly, hepatic gluconeogenesis produces glucose-6-phosphate, which together with that produced from glycogen degradation (glycogenolysis) must be hydrolyzed by glucose-6-phosphatase in the endoplasmic reticulum to be released as glucose into the circulation (Cahill et al., 1959). Therefore, tissue glucose-6- phosphatase plays a major role in the maintenance of glycemia, particularly under fasting conditions. Frontiers in Pharmacology.

Therapeutic Considerations and Risk Mitigation

Given the metabolic risks associated with diuretics, clinicians should adopt a personalized approach to antihypertensive therapy. Key strategies include:

- Baseline metabolic screening before initiating diuretics
- Use of potassium-sparing combinations to counteract hypokalemia
- Regular monitoring of fasting glucose, HbA1c, and serum electrolytes
- Consideration of alternative agents (e.g., ACE inhibitors, ARBs) in patients with high diabetes risk

In patients with resistant hypertension or heart failure, where diuretics are indispensable, these strategies can help balance blood pressure control with metabolic safety [41].

Recent Advances and Controversies in Diuretic-Induced Glucose Dysregulation

The metabolic side effects of diuretics—particularly thiazide-type agents—have long been recognized, but recent studies have provided more nuanced insights into their mechanisms and clinical relevance. Advances in molecular pharmacology, clinical trial data, and comparative drug analyses have reshaped the discourse around insulin resistance and glucose intolerance associated with diuretic therapy [42].

New Findings on Thiazide-Induced Insulin Resistance

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, have been implicated in the development of insulin resistance through multiple pathways. Recent mechanistic studies suggest that hypokalemia-induced β-cell dysfunction plays a central role [43]. Potassium depletion impairs insulin secretion and alters glucose uptake in peripheral tissues. Additionally, thiazides may activate the renin-angiotensin-aldosterone system (RAAS), leading to increased oxidative stress and inflammation—both contributors to insulin resistance [44].

A 2025 review by Di Fulvio et al. highlighted that thiazide-induced metabolic disturbances are not solely attributable to fluid and electrolyte shifts but may involve direct effects on insulin signalling pathways, including inhibition of IRS-1 phosphorylation and GLUT4 translocation. These findings underscore the need for reevaluating the long-term metabolic safety of thiazide therapy, especially in patients with prediabetes or metabolic syndrome [45, 46]

Debates on Causality vs. Correlation

Despite consistent associations between thiazide use and impaired glucose tolerance, the causal relationship remains debated. Critics argue that confounding factors—such as obesity, baseline insulin resistance, and concurrent medications—may account for the observed metabolic effects. For instance, the Study of Trandolapril/Verapamil SR and Insulin Resistance failed to demonstrate a protective effect of RAAS blockade against thiazide-induced dysglycemia, suggesting that potassium loss alone may not fully explain the phenomenon [47]. Moreover, some population-based studies have reported minimal impact on glycemic control when thiazides are used at low doses or in combination with potassium-sparing agents. These findings challenge the notion of a direct diabetogenic effect and support a more individualized approach to risk assessment [48].

Emerging Alternatives with Minimal Metabolic Impact

In response to these concerns, newer antihypertensive strategies have focused on agents with neutral or beneficial effects on glucose metabolism. Potassium-sparing diuretics such as amiloride and spironolactone have demonstrated favorable metabolic profiles. The PATHWAY- 3 trial showed that combining amiloride with hydrochlorothiazide significantly reduced the risk of glucose intolerance compared to hydrochlorothiazide alone [49].

Additionally, angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) are increasingly preferred in patients with metabolic risk, given their minimal impact on insulin sensitivity. These alternatives offer effective blood pressure control without compromising glycemic stability, aligning with current guidelines that advocate for personalized antihypertensive therapy [50].

Personalized diuretic therapy and integration with glucose-lowering agents are emerging priorities in managing hypertensive patients at risk of metabolic dysfunction. Recent studies highlight the need for targeted strategies and further research to optimize outcomes [51]. **Future Directions in Diuretic Therapy and Glucose Homeostasis**

As the global burden of hypertension and type 2 diabetes mellitus (T2DM) continues to rise, the intersection of cardiovascular and metabolic pharmacology demands renewed attention. Diuretics remain foundational in antihypertensive therapy, yet their potential to impair glucose regulation necessitates a shift toward more personalized, metabolically conscious prescribing practices. Recent advances in pharmacogenomics, clinical trial data, and therapeutic innovation offer promising avenues for refining diuretic use in high-risk populations [52].

Need for Personalized Diuretic Therapy

The heterogeneity in patient response to diuretics—both in terms of blood pressure control and metabolic side effects—underscores the importance of individualized treatment strategies. Genetic polymorphisms affecting renal sodium transporters, insulin signaling pathways, and potassium handling may influence susceptibility to diuretic-induced insulin resistance. For example, variants in the WNK1 and NEDD4L genes have been associated with altered thiazide responsiveness and glucose metabolism [53].

Personalized therapy also involves tailoring diuretic selection and dosing based on comorbid conditions. In patients with metabolic syndrome or prediabetes, low-dose thiazides or combination regimens with potassium-sparing agents may mitigate glycemic risk. Clinical decision tools incorporating metabolic risk scores and electrolyte profiles could enhance therapeutic precision [54].

Integration with Glucose-Lowering Agents

Combining diuretics with glucose-lowering agents presents a strategic opportunity to balance cardiovascular and metabolic goals. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, for instance, offer both antihypertensive and glycemic benefits through osmotic diuresis and improved insulin sensitivity. Their use alongside thiazides may reduce the need for higher diuretic doses while preserving metabolic stability [55].

Additionally, agents such as metformin and GLP-1 receptor agonists may counteract diuretic induced insulin resistance by enhancing peripheral glucose uptake and reducing inflammation. Future clinical trials should explore synergistic effects of these combinations, particularly in patients with dual diagnoses of hypertension and T2DM [56, 57].

Research Gaps and Proposed Studies

Despite growing awareness, several gaps remain in understanding and managing diuretic induced glucose dysregulation:

- Mechanistic studies are needed to delineate the molecular pathways linking electrolyte imbalance to insulin resistance.
- Longitudinal trials should assess the impact of diuretic therapy on glycemic outcomes over time, stratified by genetic and metabolic profiles [58].
- Comparative effectiveness research is warranted to evaluate newer diuretic alternatives (e.g., indapamide, amiloride) against traditional agents in terms of both cardiovascular and metabolic endpoints.
- Real-world data analyses could inform risk prediction models and guide clinical decision-making in diverse populations [59].

The integration of omics technologies, machine learning, and patient-reported outcomes into diuretic research may accelerate progress toward precision pharmacotherapy [60, 61]. Longitudinal trials should assess the impact of diuretic therapy on glycemic outcomes over time, stratified by genetic and metabolic profiles. Comparative effectiveness research is warranted to evaluate newer diuretic alternatives (e.g., indapamide, amiloride) against traditional agents in terms of both cardiovascular and metabolic endpoints. Real-world data analyses could inform risk prediction models and guide clinical decisionmaking in diverse populations. The integration of omics technologies, machine learning, and patient-reported outcomes into diuretic research may accelerate progress toward precision pharmacotherapy.

CONCLUSION:

Diuretics remain a cornerstone in the management of hypertension and cardiovascular disease due to their proven efficacy in reducing blood pressure and preventing adverse cardiovascular outcomes. However, accumulating evidence from recent clinical and mechanistic studies has highlighted their potential to disrupt glucose homeostasis, particularly through mechanisms involving hypokalemia, impaired insulin secretion, and altered peripheral glucose uptake. Thiazide and

loop diuretics have been most consistently associated with these metabolic effects, while potassium-sparing agents such as amiloride and spironolactone may offer protective benefits [62, 63].

The clinical implications of diuretic-induced glucose dysregulation are especially relevant in patients with prediabetes, metabolic syndrome, or established type 2 diabetes mellitus. In these populations, careful selection of diuretic class, dose, and combination therapy is essential to minimize metabolic risk while maintaining antihypertensive efficacy [64]. Recent trials, such as PATHWAY-3, support the use of potassium-sparing combinations to mitigate adverse glycemic effects, and emerging alternatives like SGLT2 inhibitors offer dual benefits in blood pressure and glucose control [65]. Despite these advances, several research gaps remain. The causal relationship between diuretic use and insulin resistance is still debated, and further studies are needed to elucidate the molecular pathways involved [66]. Longitudinal trials assessing the impact of diuretic therapy on glycemic outcomes, stratified by genetic and metabolic profiles, are warranted. Additionally, real-world data and pharmacogenomic insights could inform personalized treatment strategies that balance cardiovascular protection with metabolic safety [67].

In conclusion, optimizing diuretic therapy requires a nuanced understanding of its pharmacological actions and metabolic consequences. Clinicians should adopt individualized approaches that consider both blood pressure targets and glycemic stability, especially in highrisk patients [68]. Future research should aim to refine therapeutic guidelines and develop metabolically neutral or protective diuretic regimens that align with the principles of precision medicine [69].

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