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Original Article

Diuretics — A Review of the Current Knowledge

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ABSTRACT

Diuretics are medicines that make the body pass more urine and salt. They work by blocking sodium (salt) reabsorption in different parts of the kidney: • Proximal tubule – SGLT2 inhibitors, carbonic anhydrase inhibitors. • Loop of Henle – loop diuretics. • Distal tubule – thiazide and thiazide-like diuretics. • Collecting tubule – mineralocorticoid receptor antagonists. Because each type works in a different way, they can be combined for better effect. These drugs are used to treat problems like heart failure, kidney diseases, and high blood pressure. • SGLT2 inhibitors lower blood pressure, protect the heart and kidneys, and don't disturb sodium or potassium levels. • Acetazolamide helps in acute heart failure. • Loop diuretics reduce high blood pressure and extra fluid in the body, but sometimes cause electrolyte imbalance. • Thiazide diuretics mainly lower blood pressure, but can cause low sodium (hyponatremia) and low potassium (hypokalaemia). • Mineralocorticoid receptor antagonists also protect the heart and kidneys and reduce blood pressure, but may cause high potassium (hyperkalaemia).

Keywords: Diuretics, Classification of diuretics, SGLT2 Inhibitors, Carbonic anhydrase inhibitors, Loop diuretics, Thiazide diuretics. Mineralocorticoid receptor antagonist, Types, Mechanism of action

INTRODUCTION

This article explains the main types of diuretics (water pills) and how they are used to treat kidney problems and high blood pressure. Diuretics are medicines that help the body get rid of extra water and salt by making you urinate more. Different types of diuretics work in different ways, so doctors can combine them for better results. These medicines act on different parts of the kidney's filtering system — the proximal tubule, loop of Henle, distal tubule, and collecting tubule [1].

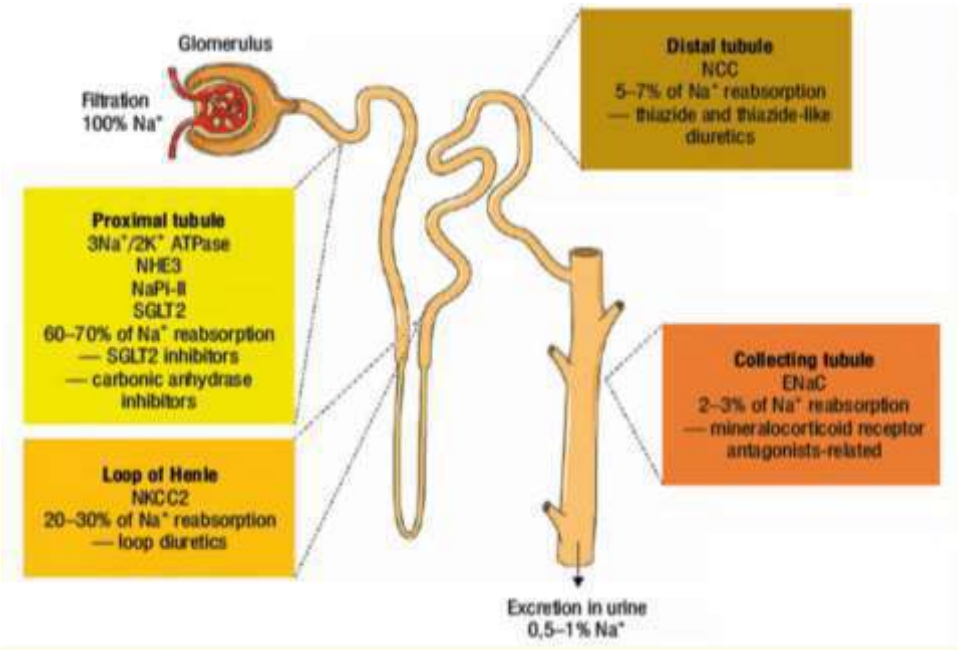

Figure 1 shows how the kidneys control the balance of sodium (salt) in the body and where each type of diuretic works.

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- NHE3 – sodium-hydrogen exchanger
- NaPi-II – sodium-phosphate transporter
- SGLT2 – sodium-glucose transporter
- NKCC2 – sodium-potassium-chloride transporter
- NCC – sodium-chloride transporter
- ENaC – epithelial sodium channel

Classification of Diuretics:

1. SGLT2 Inhibitors:

- How they work:

SGLT2 inhibitors are medicines that stop the kidneys from reabsorbing too much sugar (glucose) and salt (sodium) in the proximal tubule of the nephron. Normally, SGLT2 proteins reabsorb about 97% of the sugar filtered by the kidneys. They do this by moving glucose together with sodium (1 glucose + 1 sodium). When SGLT2 inhibitors are used, more sugar and sodium leave the body in urine. These drugs also reduce the activity of another transporter (NHE3), which further decreases sodium reabsorption.

- Main effects:

Increase salt (natriuresis) and urine (diuresis) output. Cause weight loss at first due to water loss. Later, weight loss happens because they reduce fat storage and increase fat burning. Remove water both from inside and outside cells, but not as strongly as loop diuretics. Unlike other diuretics, they do not trigger the body to increase renin or activate the sympathetic nervous system**.**

Effect of sodium on body:

They lower sodium levels stored in tissues, including skin and blood vessel linings (glycocalyx). This improves the flexibility and function of blood vessels, helps them produce nitric oxide (a substance that widens blood vessels), and improves blood flow.

- Impact on blood pressure and heart:

Reduce blood pressure mildly (systolic by about 5 mmHg, diastolic by about 1–2 mmHg). Lower both day and night blood pressure. Improve blood vessel health.

- Kidney and heart protection:

Large studies have shown that SGLT2 inhibitors:

Slow the worsening of chronic kidney disease (CKD), even in people without diabetes. Reduce the risk of heart failure, heart-related death, and overall death. Reduce albumin (protein) in urine, which is a sign of kidney protection.

- Important studies:

DAPA-CKD (dapagliflozin): Showed 44% lower risk of severe kidney decline, dialysis, or kidney-related death. Also reduced heart failure events and overall death.

EMPA-KIDNEY (empagliflozin): Showed reduced kidney disease progression, fewer heart-related deaths, and fewer hospitalizations.

- Why kidney function (eGFR) drops at first:

When starting these drugs, eGFR falls slightly (about 3–4 mL/min/1.73 m^2). This is not harmful—it is a protective effect. It happens because the drug lowers the pressure inside kidney filters (by narrowing the incoming vessels and widening the outgoing ones). Over time, this protects kidneys and slows their decline.

- Electrolytes (Sodium & Potassium):

Unlike other diuretics, SGLT2 inhibitors do not disturb sodium or potassium levels. In fact, they may even reduce the risk of high potassium (hyperkalemia), especially in patients taking drugs that affect the renin–angiotensin system or mineralocorticoid receptor antagonists.

- Simple Summary:

SGLT2 inhibitors are medicines that make the kidneys pass more sugar and salt into the urine. They help lower blood pressure a little, reduce body weight, protect the kidneys and heart, and don't upset the balance of sodium and potassium. They are useful in both diabetic and non-diabetic kidney disease, and their benefits have been proven in large clinical trials.

2. Carbonic Anhydrase Inhibitors:

The main drug in this group is acetazolamide**.**

- How it works:

In the kidney's proximal tubule, acetazolamide reduces the movement of hydrogen ions. Because of this, less sodium is taken back into the body (via the sodium-hydrogen exchanger NHE3). As a result, more sodium and water are passed out in urine.

- Uses:

Acetazolamide is used to treat glaucoma (high pressure in the eye), altitude sickness**,** and sometimes acute heart failure.

- Study evidences:

In the ADVOR trial with 519 patients who had acute heart failure, doctors gave acetazolamide (500 mg/day) together with a loop diuretic for 3 days. Compared to using a loop diuretic alone, patients on the combination had more salt and water loss and less fluid build-up**.**

- Duration of use:

Usually, treatment lasts only about 3 days**.**

- Side effects:

Acetazolamide can cause:

- tingling feelings in the skin (paresthesia**)**
- changes in taste (dysgeusia**)**
- passing urine too often (polyuria**)**
- tiredness **(**fatigue)

- In short:

Acetazolamide is a short-term diuretic useful in treating acute heart failure, but it can cause some annoying side effects.

3. Loop Diuretics:

- Examples: furosemide, bumetanide, torsemide.
- They work in the loop of Henle by blocking the Na-K-Cl transporter (NKCC2)**.**
- This makes the kidneys pass out more sodium, potassium, chloride, and water.
- Main uses:
  - Reduce swelling and fluid overload in heart failure and kidney disease.
  - Help lower blood pressure, especially in people with poor kidney function.

- Benefits:
  - Effective at reducing excess body water.
  - Lower blood pressure by about 8/4 mmHg**.**
  - Electrolyte problems (low sodium or potassium) are possible but not very common.

- Problem: Resistance can develop (medicine stops working well). Causes include:
  - Not enough drug reaching the kidneys
  - Poor absorption
  - Kidney changes (e.g., reduced blood flow, tubular changes)
  - Activation of other sodium reabsorption pathways (like ENaC channels in collecting duct).

- Solution for resistance:
  - Increase dose or frequency
  - Combine with another diuretic that works elsewhere in the kidney (e.g., thiazides, ENaC blockers like amiloride).

4. Thiazide and Thiazide-Like Diuretics (Simplified):

- How they work:
- These medicines block a protein (sodium-chloride symporter, NCC) in the first part of the distal tubule of the kidney. This makes the kidney lose more sodium and chloride in urine, which also reduces water in the body.
- Blood pressure control:
- Thiazide diuretics are one of the five main drug groups used for high blood pressure.
- Studies show they lower blood pressure by about 9 mmHg (systolic) and 4 mmHg (diastolic).
- Thiazide-like diuretics (e.g., chlorthalidone, indapamide) usually work better than thiazide diuretics (e.g., hydrochlorothiazide).
- Use in kidney disease (CKD):
- High blood pressure in CKD is usually hard to control, so most patients need 2 or more medicines.

- In one study, chlorthalidone lowered systolic blood pressure by about 11 mmHg and cut protein leakage in urine by half in patients with reduced kidney function (eGFR 15–30).
- Other thiazide(-like) drugs also lowered blood pressure in CKD patients.
- In polycystic kidney disease (ADPKD), thiazides do not worsen disease progression, so they are considered safe.
- Side effects and risks:
- Electrolyte problems:

  - Hyponatremia (low sodium in blood):
    - Quite common (about 14% of patients, especially older people).
    - Can happen early (within the first 3 weeks, sometimes even in 2 days).
    - Symptoms: nausea, vomiting, confusion, drowsiness, seizures, or coma.
    - Risk factors: older age, low body weight, high dose.
    - Can happen even with small doses (12.5 mg hydrochlorothiazide).
    - Prevention: regular sodium blood tests (after 2–3 weeks and yearly), patient education, and avoiding excess water (>2.5 L/day).
    - If it occurs → stop the drug, do not restart, and use a different diuretic (like loop diuretics).
  - Hypokalemia (low potassium in blood):
    - Happens because more sodium reaches the collecting duct, leading to potassium loss in urine.
    - In elderly studies, seen in 3–4% of patients.
    - Risk is similar across thiazide and thiazide-like diuretics.

- Skin cancer risk:

  - Hydrochlorothiazide may slightly increase the risk of skin cancers because it makes the skin more sensitive to sunlight.
    - Higher risk with long-term use (over 10 years) and high doses.
    - Cancers linked: squamous cell carcinoma, melanoma, and basal cell carcinoma.
  - Indapamide does not increase skin cancer risk.
  - Patients using hydrochlorothiazide long-term should:
    - Avoid too much sun,
    - Have regular skin check-ups.

- Key points to remember:
- Thiazide and thiazide-like diuretics are effective blood pressure medicines.
- They are useful even in chronic kidney disease.
- Main risks: low sodium (hyponatremia), low potassium (hypokalemia), and possible skin cancer with hydrochlorothiazide.
- Monitoring and preventive care are important.

5. Mineralocorticoid Receptor Antagonists (Mras):

- Mechanism of action:

- MRAs block aldosterone from binding to its receptor.
- This reduces sodium reabsorption in the collecting tubule by lowering ENaC activity.
- Additional effects: anti-fibrotic, anti-inflammatory, antioxidant, and reduction of kidney scarring.

- Types:

- Steroidal MRAs: spironolactone, eplerenone
- Non-steroidal MRA: finerenone (newer, more selective)

- Clinical benefits:

1. Hypertension (especially resistant hypertension)-

- Steroidal MRAs lower systolic BP by ~8 mmHg and diastolic by ~3 mmHg.
- In CKD patients with resistant hypertension, spironolactone lowers systolic BP by ~11 mmHg.

2. Chronic kidney disease (CKD)-

- Steroidal MRAs reduce proteinuria when combined with renin–angiotensin system inhibitors.

- Finerenone slows CKD progression in diabetic kidney disease (FIDELIO-DKD trial).

3. Heart failure (HF)-

- MRAs improve prognosis in HF with reduced ejection fraction.
- Finerenone also reduces risk of HF hospitalization and cardiovascular complications.

Evidence for finerenone-

- FIDELIO-DKD study (5,734 patients with CKD + diabetes):

  - Slowed CKD progression
  - Reduced kidney failure risk
  - Lowered cardiovascular events
  - Reduced albuminuria by 31%

- Safer potassium profile compared to spironolactone
- Confirmed in large meta-analyses

  - Side effects-

- Hyperkalemia (high potassium) → main risk

  - More common with spironolactone than eplerenone
  - Finerenone has lower risk than steroidal MRAs

- Hyponatremia (low sodium) → less frequent, but possible
- Risk depends on dose and kidney function

  - Key takeaway

- MRAs provide antihypertensive, kidney-protective, and heart-protective effects.
- Finerenone is safer (less hyperkalemia) and especially useful in CKD with diabetes.
- Careful monitoring of potassium and sodium is essential.

CONCLUSION:

SGLT2 inhibitors also help the body get rid of extra water and salt (they act like diuretics). Treating too much fluid in the body can slow down kidney disease. For patients with kidney disease and very low kidney function (eGFR 15–30), chlorthalidone works well to lower blood pressure and also lowers protein in the urine. People with polycystic kidney disease can safely use thiazide or thiazide-like diuretics to control blood pressure. Low sodium in the blood (hyponatremia) is an important side effect of thiazide and thiazide-like diuretics.

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