Abstract. – As the prevalence of diabetes rises, the use of antidiabetic drugs becomes more frequent. Thus, focusing on the effects of these drugs on water-sodium balance and electrolyte regulation is necessary. This review discusses the effects and the mechanisms behind them. Several sulfonylureas, such as chlorpropamide, methanesulfonamide, and tolbutamide, exhibit water-retaining properties. Other sulfonylureas, such as glipizide, glibenclamide, acetohexamide, and tolazamide, are not antidiuretic or even diuretic. Numerous clinical studies showed that metformin can reduce serum magnesium concentrations and may have an effect on the cardiovascular system, but the specific mechanism remains to be discussed. Different opinions exist about the mechanisms of thiazolidinedione-induced fluid retention. Sodium-glucose cotransporter 2 inhibitors can cause osmotic diuresis and natriuresis and elevated serum potassium and magnesium concentrations. Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors can enhance urine sodium excretion. At the same time, increased urinary sodium caused by sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors reduce blood pressure and plasma volume, thereby protecting the heart. Insulin has a sodium-retaining effect and is also associated with hypokalemia, hypomagnesemia, and hypophosphatemia. Several of the aforementioned pathophysiological changes and mechanisms have been discussed, and conclusions have been drawn. However, further investigation and discussion are still warranted.

Key Words: Antidiabetic drugs, Electrolyte, Water-sodium balance, Insulin, Hypokalemia.

Introduction

Type 2 diabetes mellitus (T2DM) has become a major medical issue due to its growing global prevalence, but many anti-diabetic drugs, once sanctioned, have been withdrawn from use by the U.S. Food and Drug Administration. Sulfonylureas achieve hypoglycemia by stimulating insulin release from pancreatic islet cells. They also reduce hepatic insulin clearance, decrease glucagon secretion, and improve insulin sensitization in peripheral tissues of patients with type 2 diabetes. Thiazolidinediones (TZDs) act as a peroxisome proliferator-activated receptor γ subtype (PPAR-γ) activator and can directly reduce insulin resistance. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) inhibit glucose absorption from the kidney’s proximal tubule (PT) and hence cause glycosuria. Glucagon-like peptide-1 (GLP-1) is a substance secreted by the intestines that promotes insulin secretion. It promotes insulin secretion by pancreatic β cells in a glucose-dependent manner, which is less likely to induce hypoglycemia and inhibits glucagon secretion by pancreatic α cells. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) enhance the action of GLP-1 by activating the GLP-1 receptor. Dipeptidyl peptidase-4 inhibitors (DPP-4i) increase the level of GLP-1 by inhibiting the inactivation of GLP-1. GLP-1RAs and DPP-4i thus lower glucose levels, while being widely used in recent years due to their minimal side effects. All of these drugs lower blood sugar while altering the water-sodium balance and electrolyte levels to a greater or lesser extent. Maintaining water and electrolyte levels within standard ranges is of
great importance for cellular activity, biological function and survival. Abnormalities in water and electrolytes not only cause sodium retention, hypomagnesemia, hypokalemia, and hypophosphatemia but also further increase the risk of disease in vital organs such as the heart and kidneys. In this narrative review of the literature, we present and discuss the mechanisms of the effects of antidiabetic drugs on water-sodium balance and electrolyte regulation.

The key role of the kidneys in water-sodium balance and electrolyte homeostasis are briefly outlined below. Figure 1 shows a partial display of renal tubular reabsorption processes and possible sites of action of antidiabetic drugs. Most of the Na and water is reabsorbed at the PT. In the first half of the PT, the Na\(^+\)-K\(^+\)-ATPase at the basolateral membranes of the epithelia reduces the intracellular Na\(^+\) concentration. The Na\(^+\)-H\(^+\) exchanger-3 (NHE3), sodium-glucose/amino acid/phosphate/Cl\(^-\) cotransporter at the apical membrane then convert Na\(^+\) from the tubular fluid into the epithelia. The Na\(^+\)-K\(^+\)-ATPase, in turn, transfers it to the interstitial fluid, where Na\(^+\) enters the blood due to the increased hydrostatic pressure of the interstitial fluid. SGLT-2 and GLP-1R are both found in the PT\(^0\). In the second half of the PT, the Cl\(^-\)-HCO\(_3\)^- exchanger at the apical membrane allows Cl\(^-\) to enter the epithelia and the K\(^+\)-Cl\(^-\) cotransporter at the basolateral membrane transfers it to the interstitial fluid. The Cl\(^-\) in the tubular fluid can be reabsorbed by the paracellular pathway due to the concentration difference, and then Na\(^+\) can be reabsorbed along the potential gradient by the paracellular shunt. In the PT and thin descending limbs, aquaporin-1 is abundantly

Figure 1. Partial display of renal tubular reabsorption processes and possible sites of action of antidiabetic drugs. PT, proximal tubule; tDL, thin descending limb; tAL, thin ascending limb; TAL, thick ascending limb; DCT, distal convoluted tubule; ADH, Antidiuretic hormone; ANP, Atrial natriuretic peptide.
present in the apical and basolateral membranes\textsuperscript{11}. Electrolyte reabsorption causes the osmotic pressure of the intercellular fluid to increase; thus, water is reabsorbed through aquaporin-1 and paracellular pathways under the action of osmotic pressure. Compared with the thin descending limb, the thin ascending limb is more permeable to NaCl and has a 100-fold lower water permeability; thus, NaCl can enter the interstitial fluid \textit{via} facilitated diffusion. Approximately 25-30\% of net sodium recovery is done at the thick ascending limb. Na\textsuperscript{+}-K\textsuperscript{+}-2Cl\textsuperscript{−} cotransporter (NKCC2) at the apical membrane transports Na\textsuperscript{+}, K\textsuperscript{+}, and Cl\textsuperscript{−} along a concentration gradient. Na\textsuperscript{+} and Cl\textsuperscript{−} enter the interstitial fluid \textit{via} the Na\textsuperscript{+}-K\textsuperscript{+}-ATPase and Cl channel, but K\textsuperscript{+} goes back into the tubular fluid along the concentration. Positive ions, such as Na\textsuperscript{+}K\textsuperscript{+}Ca\textsuperscript{2+}, are passively reabsorbed by the paracellular pathway, resulting in potential differences caused by K\textsuperscript{+}. In the distal convoluted tubule, Na\textsuperscript{+}-Cl\textsuperscript{−} cotransporter mainly transfers Na\textsuperscript{+} and Cl\textsuperscript{−}. The collecting duct is classified into the inner medullary collecting duct (IMCD), outer medullary collecting duct and cortical collecting duct. Here, Na\textsuperscript{+} uses the concentration difference generated by Na\textsuperscript{+}-K\textsuperscript{+}-ATPase to cross into the epithelial cells \textit{via} the epithelial Na channel (ENaC)\textsuperscript{12}. Water is reabsorbed through aquaporin-2 (AQP2) in the apical membrane and subapical vesicles in the principal cells and aquaporin-3,4 in the basolateral membrane. Antidiuretic hormone (ADH) regulates water reabsorption by controlling the amount of AQP2\textsuperscript{22}. The renin-angiotensin-aldosterone system (RAAS) plays an essential role in maintaining the water–sodium balance of the human body\textsuperscript{13}. Aldosterone ultimately acts on ENaC and Na\textsuperscript{+}-K\textsuperscript{+}-ATPase in the epithelia to increase Na\textsuperscript{+} and water reabsorption and K\textsuperscript{+} excretion\textsuperscript{14}. Atrial natriuretic peptide (ANP) exerts natriuretic and diuretic effects by inducing a signaling cascade expressed along the glomerulus and nephron. ANP mainly decreases Na reabsorption by suppressing ENaC and cyclic nucleotide-gated cation channels in the epithelial cells of the medullary collecting ducts\textsuperscript{15}. ANP also inhibits the secretion of renin, aldosterone, and ADH\textsuperscript{16}.

**Sulfonylureas**

Sulfonylureas have been commercially available since the 1950s, but their use remains controversial\textsuperscript{18}. The effect of sulfonylureas on water balance is either diuretic or anti-diuretic\textsuperscript{19}. Several sulfonylureas, such as chlorpropamide and methanesulfonamide, can cause water retention\textsuperscript{20}. Some studies\textsuperscript{21} reported that pharmacological doses of chlorpropamide can directly increase the permeability of terminal IMCD to water without ADH. However, chlorpropamide can induce hyponatremia in approximately 4-6\% of patients by potentiating the ADH effect. The risk of hyponatremia development is greater in older patients who concomitantly use diuretics. Hyponatremia can be induced by lowering renal clearance of free water (C\textsubscript{H2O}) with the addition of Tolbutamide\textsuperscript{22}. Other sulfonylureas, such as glipizide, glibenclamide, acetohexamide, and tolazamide, are neither diuretic or anti-diuretic. The ingestion of sulfonylureas that lack antidiuretic properties can increase C\textsubscript{H2O} by enhancing Na\textsuperscript{+}, K\textsuperscript{+}, and Cl\textsuperscript{−} reabsorption at the thin ascending limb (tAL) and thick ascending limb (TAL)\textsuperscript{23}. Additionally, increased adrenaline secretion caused by sulfonylurea-induced hypoglycemia may be associated with hypokalemia, hypomagnesemia, and hypophosphatemia in some cases\textsuperscript{23}.

**Metformin**

Hypomagnesemia often occurs in patients with untreated diabetes. Hyperglycemia can cause urinary magnesium excretion. Hypomagnesemia is associated with insulin resistance and the development of chronic complications of diabetes mellitus\textsuperscript{24}. Meanwhile, the majority of the studies\textsuperscript{25-28} showed that the use of metformin leads to a decrease in serum magnesium concentrations. A cohort study\textsuperscript{25} that included 395 patients with T2DM reported that plasma magnesium concentrations were reduced in patients using metformin. A longitudinally observed Fremantle Diabetes Study\textsuperscript{26} Phase I that enrolled 940 non-insulin-treated patients, showed that 19\% of patients had serum magnesium <0.70 mmol/L. Serum magnesium concentrations were lower in patients on metformin alone or in combination with sulfonylurea than in those on diet alone. Gastrointestinal losses due to increased duration of metformin treatment may be responsible for hypomagnesemia. A case report\textsuperscript{27} described a patient who presented with severe and symptomatic hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia secondary to metformin-induced diarrhea. In a previous study\textsuperscript{28}, patients using metformin showed decreased magnesium excretion but remained to have hypomagnesemia and hypercalciuria. Although metformin
Water-sodium balance and electrolyte regulation

Thiazolidinediones

Fluid Retention

As the most common and serious side effect of TZDs, the incidence of fluid retention ranges from 7% with TZDs monotherapy to 15% in combination with insulin. Some studies suggested that TZD-induced fluid retention is due to increased sodium and water reabsorption in the kidneys. However, mechanisms of renal sodium reabsorption are controversial. In a recent study, mRNA expression of α, β, and γ isoforms of ENaC and AQP2, and aquaporin 3 (AQP3) in the renal medulla was significantly increased (by 1.5 to 2-fold) in response to pioglitazone. The increased expression of these channels caused higher reabsorption of sodium and water in the kidney. In addition, rosiglitazone increased AQP2, alpha epithelial Na+ channel (αENaC), and AQP3 expression in mouse IMCD, human embryo kidney, and the renal medulla of type 2 diabetic rats. In the study by Tahara, pioglitazone caused a decrease in urinary sodium excretion, which supports the theory that increased ENaC gene expression leads to increased Na+ reabsorption. By contrast, the level of sodium in the plasma is reduced. Moreover, the urine volume markedly decreased and urinary osmolality increased. The above water retention phenomenon may be due to the increased expression of AQP which increases water reabsorption. ENaC, a regulator of body fluid volume, is necessary for the kidney to absorb sodium and plays a role in edema formation. In view that TZDs are PPAR-γ activators, a study found that TZDs-induced fluid retention due to enhanced expression of ENAC-γ by PPAR-γ. Another study found that PPAR-γ enhances ENaC by upregulating serum glucocorticoid regulated kinase-1 in collecting duct cells. However, several studies have refuted the inference that TZD enhances sodium transport by activating ENaC, as follows: (1) based on some observations, PT may be another target for TZD action. (2) Vallon et al. demonstrated that mice with inactivated ENaC had nearly the same fluid retention levels after TZDs treatment as controls. Patch clamp studies on collecting duct cells revealed that TZDs activated a non-selective cation channel, but not ENaC and even inhibited ENaC activity in mice. (3) In Sprague-Dawley rat kidneys, TZD did not increase the expression of any ENaC subunits. (4) The phenomenon of “aldosterone escape”: aldosterone enhances ENaC activity in the collecting duct while inhibiting sodium reabsorption in other parts of the nephron. Thus, activation of ENaC alone does not usually cause significant sodium retention and edema.

(5) Protein expression of the α-1 subunit of Na⁺-K⁺-ATPase, NHE3 and NKCC2 is enhanced in rosiglitazone treated Sprague-Dawley rat kidneys. According to the distribution of these carriers along the nephron, another review in 2013 indicated that rosiglitazone is more likely to act on the PT or loop of Henle than on the collecting duct or distal tubule. The effect of PPAR agonists on Na⁺ transport is mediated by the nongenomic PPAR-c-Src-EGFR-extracellular signal-regulated kinase mechanism found in PT. A similar conclusion was obtained in a review conducted in 2015. In the review conducted in 2013, a specific mechanism leading to increased sodium reabsorption was mentioned. The negative potential generated by chloride secreted into the renal tubules may inhibit sodium reabsorption. Pioglitazone inhibits chloride ion secretion by the cystic fibrosis transmembrane conductance regulator chloride channels. Some studies considered that vascular hyperpermeability was also a prominent factor in TZD-induced fluid retention. Rosiglitazone...
selectively enhanced vascular permeability in retina and adipocytes\textsuperscript{42}. The vascular endothelial growth factor activated by PPAR-\(\gamma\) ligands may contribute to the increase in vascular permeability\textsuperscript{32}. TZDs may lead to congestive heart failure in patients with diastolic dysfunction due to water and sodium retention. However, pioglitazone does not affect left ventricular function because it ameliorates diastolic dysfunction and augments myocardial insulin sensitivity\textsuperscript{43}.

**Effects on Electrolytes**

A study\textsuperscript{44} in an animal model of T2DM and obesity suggested that insulin resistance could increase circulating visfatin levels and thus disrupt electrolyte balance, causing hypomagnesemia, hyperkalemia, and hyponatremia, while rosiglitazone improved insulin resistance, decreased circulating visfatin levels, and reversed the changes in electrolyte levels. By contrast, a case report suggested that the inappropriate ADH secretion-related hyponatremia in an elderly woman with diabetes mellitus may have been due to rosiglitazone\textsuperscript{45}. Two clinical studies\textsuperscript{46,47} in patients with T2DM and in glucose-intolerant populations both concluded that pioglitazone increased serum magnesium levels. Pioglitazone also increased the concentration of free magnesium in rat adipocytes\textsuperscript{48}. Rosiglitazone prevented and attenuated hypomagnesemia and hypokalemia induced by sirolimus in Wistar rats\textsuperscript{49}. Pioglitazone and rosiglitazone slow down the development of atherosclerosis and reduce the incidence of cardiovascular diseases such as myocardial infarction\textsuperscript{41}. Combined with the positive effect of magnesium ions on the cardiovascular system, we hypothesize that the improvement of cardiovascular function by rosiglitazone and pioglitazone is partly due to the increased concentration of magnesium ions.

**SGLT2 Inhibitors**

**Natriuresis and Osmotic Diuresis**

SGLT2i increases urinary glucose and sodium excretion by blocking glucose and sodium reabsorption\textsuperscript{50}. However, the increase in urinary sodium is temporary. No change in urinary sodium excretion after eight weeks of treatment in type 1 diabetic patients is considered an equilibrium formation\textsuperscript{51}. In addition, the transient natriuretic effect is due to increased sodium reabsorption in other parts of the renal unit. Increased RAAS activity facilitates this process. Some scholars\textsuperscript{52} suggest that SGLT2i treatment briefly activates the systemic RAAS but not the intrarenal RAAS in patients with T2DM. In other words, plasma renin activity and serum aldosterone levels are increased, but renal angiotensinogen expression does not change. A sodium balance is established after 2-3 days of SGLT2i administration based on a reduction in systemic sodium levels\textsuperscript{53}. SGLT2i-induced glucosuria leads to osmotic diuresis, again transiently, and does not cause sustained changes in osmolality\textsuperscript{54}. Patients on canagliflozin and empagliflozin had an increase in 24-h urine output of approximately 300 mL/d after 1 day of treatment, returning to baseline levels after several weeks\textsuperscript{51}. Different findings\textsuperscript{51,54,55} have been reported on plasma volume in patients with T2DM treated with SGLT2i. A pooled analysis of several randomized controlled trials\textsuperscript{54} found a 9.6% reduction in plasma volume after 24 weeks of dapagliflozin use. A comparison study\textsuperscript{56} on fluid distribution showed that SGLT2i dapagliflozin mainly reduced extracellular water with a slight increase in urine volume. The effect of SGLT2i on the distribution of body fluids is different from that of furosemide and tolvaptan. To sum up, SGLT2i rapidly reduces a certain amount of plasma volume at first, but gradually stabilizes\textsuperscript{51}.

SGLT2i treatment improves fasting and postprandial glucose, fasting lipids, blood pressure, body weight, serum uric acid, and arterial stiffness, all of which are harmful cardiovascular factors. SGLT2i protects the heart and kidney by affecting diuresis, fluid and sodium retention, inflammation, oxidative stress, myocardial function, and vascular resistance\textsuperscript{56}. Among these, osmotic diuresis and natriuresis act as a bridge. According to the available studies\textsuperscript{51,53,56}, natriuretic sodium should be important for SGLT2i to lower blood pressure and also reduce atherosclerosis as a result. Increased urinary sodium also causes a decrease in plasma volume, thereby reducing cardiac preload, weakening myocardial expansion, and reducing the incidence of arrhythmias. Combination treatment with ipragliflozin + pioglitazone attenuated pioglitazone-induced fluid retention by ipragliflozin-induced osmotic diuresis\textsuperscript{54}. Experimental and clinical evidence generally suggests one of the several putative mechanisms of natriuresis and osmotic diuresis that might explain the beneficial properties of SGLT2i on the risk of mortality\textsuperscript{57}.

**Effects on Electrolytes**

Hyperkalemia is among the risks initially claimed for SGLT2i in its early use. Nevertheless, subsequently released data\textsuperscript{58} suggest that SGLT2i is not associated with an increased risk of hyper-
kalemia. A high dose of canagliflozin causes a minor increase in serum potassium concentration. A clinically significant increase in potassium levels was documented with canagliflozin 300 mg/d, particularly in patients having decreased glomerular filtration rate and those taking agents affecting potassium excretion. A slight but nonsignificant increase in potassium levels was observed with dapagliflozin. The mechanisms involved in causing the small increase in serum potassium levels due to SGLT2i are as follows. The mechanism that increases potassium excretion and thus decreases serum potassium is currently twofold. One is that SGLT2i-induced natriuresis and osmotic diuresis increase tubular flow rates in the distal convoluted and collecting tubules, while increasing aldosterone levels due to lower plasma volume, which increases potassium excretion. The second is that elevated glucagon levels probably facilitate diuresis in the distal convoluted and collecting tubules. Also, glucagon is speculated to be an intestinal factor that contributes to increased renal potassium excretion. Conversely, elevated serum potassium is caused by insulin-promoting potassium entry into cells. The decrease in insulin concentration after SGLT2i dosing could lead to the repartition of potassium from intracellular to extracellular. Despite the negligible increase in serum potassium, careful monitoring of potassium homeostasis should be prompted in patients with renal impairment and medications that predispose them to hyperkalemia. Randomized controlled meta-analyses have shown that SGLT2i dose dependency increased serum magnesium levels. Similar to the small increase in serum potassium, serum magnesium due to SGLT2i is also affected by a number of factors and eventually increases slightly. Hypermagnesuria and hypomagnesemia induced by downregulation of the transient receptor potential melastatin-6 (TRPM6) ion channel observed in T2DM rats are thought to be related to insulin resistance. SGLT2i improves insulin resistance and thus reduces urinary magnesium excretion via TRPM6. SGLT2 may also decrease insulin and increase glucagon levels. Decreased insulin levels allow magnesium ions to be transferred from intracellular to extracellular, while glucagon increases magnesium reabsorption in the distal renal tubules. Natriuresis and osmotic diuresis can induce a decrease in plasma volume, resulting in a relatively slight increase in serum magnesium concentration. They also increase aldosterone concentrations which lead to increased magnesium excretion.

**GLP-1RAs**

A study found that mice treated with liraglutide promoted ANP release by activating atrial cardiomyocytes. ANP induced cGMP-mediated smooth muscle relaxation, increased urinary sodium excretion, and also lowered blood pressure as a result. Moreover, liraglutide did not affect the natriuresis of ANP knockout mice. However, another study found that injection of native GLP-1 significantly increased urine sodium excretion in humans, but no change in proANP concentration. The natriuretic effect of GLP-1 is speculated to be unlikely caused solely by increased ANP secretion. The difference between the results of the above two studies may be attributed to the difference between native GLP-1 and liraglutide, or the effect of liraglutide on rodents could not be observed in humans. With regard to the mechanism of GLP-1’s diuretic and natriuretic actions, previous studies suggested that it is mediated by changes in renal hemodynamics and downregulation of NHE3 activity in the proximal renal tubules. Conversely, in heart failure patients with reduced ejection fraction, liraglutide treatment reduced plasma type A and B natriuretic peptide levels and urine sodium content after 24 weeks.

**DPP-4 Inhibitors**

A study found an increase in sodium excretion (65%) in rats treated with DPP-4i Lys Z(NO2)-pyrrolidide for 7 days. Accordingly, DPP-4i increases urine output by 70% due to a decrease in sodium and water reabsorption. Redistribution of NHE3 is closely related to water-salt regulation and water reabsorption by PT, and DPP4i is associated with reduced NHE3 protein expression. As previously mentioned, GLP-1 also promotes natriuresis in the kidney. Therefore, DPP-4i–mediated natriuresis may be mediated by active GLP-1 levels. However, in the study by Muskiet et al, linagliptin enhanced GLP-1 concentrations, yet urinary pH and fractional excretion of endogenous lithium remained unaffected, in contrast to the theory that linagliptin inhibits NHE3. They did not find a link between linagliptin-induced changes in the fractional excretion of sodium and GLP-1. But they speculated that DPP-4i might promote sodium excretion at least in part through other pathways independent of the GLP-IR signaling pathway and NHE3. Moreover, DPP-4i...
promotes distal tubular natriuresis while increasing levels of a bioactive stromal cell-derived factor-1 α1 (SDF-1α1-67). SDF-1α1-67, a chemotactic factor with proven natriuretic effects in studies70, is augmented by sitagliptin.

Insulin

Sodium consumption in patients with poorly controlled diabetes is generally speculated to be due to glucosuria and the resulting osmotic diuresis or marked ketonuria. But insulin deficiency itself can also lead to excessive sodium consumption71. Therefore, studies72 showed that insulin has a sodium-retaining effect during hyperglycemia, which may be relevant for maintaining sodium balance in patients with uncontrolled T2DM. Because insulin can directly increase ENaC activity, the sodium-phosphate cotransporter, NHE3, and Na+-K+-ATPase increase sodium reabsorption in the PT, thick ascending limb, and distal tubule, including the collecting duct73. The intravenous administration of glucose can cause hyperinsulinemia, resulting in sudden hypokalemia that is caused by the massive intracellular transfer of potassium74. Further mechanisms are as follows: after binding to specific cell-surface receptors, insulin-releasing in vivo not only facilitates glucose uptake by target tissues but also stimulates K+ uptake by increasing Na+-K+Cl- reabsorption. The use of metformin may lead to a reduction in serum potassium levels. In addition, insulin-mediated K+ uptake is differentially regulated75. The impact of insulin on Na+-K+-ATPase is shown to be mainly regulated in the short term. Na+-K+-ATPase α1 translocates to the plasma membrane and internalizes into the cytoplasm, and insulin regulates the efficiency of transport by changing its molecular conformation. In addition, the activity of Na+-K+-ATPase may also be regulated in the long term. Insulin may promote mRNA transcription and protein expression levels of Na+-K+-ATPase α1 through two degradation pathways, the ubiquitin-proteasome and the autophagy-lysosome system76. Another mechanism by which insulin affects plasma potassium ion concentration is through the activation of the Na+-H+ exchanger-1. The Na+-H+ exchanger-1 exchanges intracellular H+ with Na+ from the extracellular fluid, and Na+ then exchanges with K+ in the extracellular fluid through Na+-K+-ATPase77. In addition, severe insulin-induced hypoglycemia induces the additional secretion of epinephrine. Epinephrine can also stimulate cellular potassium uptake by activating Na+-K+-ATPase78. A case report79 of a 47-year-old man with T2DM who attempted suicide with 2,100 U of insulin injected subcutaneously was presented. The man developed hypokalemia, hypophosphatemia, and hypomagnesemia within 24 h of his suicide attempt. Hypomagnesemia and hypophosphatemia may be due to the rapid increase in the accumulation of magnesium and phosphorus in cells by the addition of insulin in vivo. Researchers79 showed that insulin induces the transfer of magnesium from plasma to erythrocytes both in vivo and in vitro. In patients with diabetes, the urinary excretion of magnesium increases with insulin dose independent of glucosuria. Also, insulin administration in normal men results in increased magnesium excretion79.

On the contrary, another study80 showed that insulin use was positively correlated with plasma Mg2+ levels. A trend toward higher plasma Mg2+ levels was observed in patients taking insulin compared with those not requiring insulin therapy. The mechanism probably is that insulin stimulates the activity of renal TRPM6, particularly through insulin receptor substrate, via a signaling cascade that ultimately increases cell membrane abundance of this channel and renal Mg2+ reabsorption81.

Conclusions

Antidiabetic drugs change water and electrolyte metabolism. Moreover, diabetes mellitus and its complications inherently cause electrolyte disorders; thus, the changes in water and electrolytes in patients with diabetes are worthy of attention and discussion. Several sulfonylureas possess water-retaining properties by acting on different sites and increasing water reabsorption; others are not antidiuretics or even diuretics by increasing Na+-K+-Cl- reabsorption. The use of metformin may lead to a reduction in serum magnesium concentrations, but the mechanism is not well understood. Although the mechanism of TZD-induced fluid retention is vigorously debated, fluid retention is the most common and severe adverse effect of TZD. SGLT2i can result in osmotic diuresis caused by glucosuria and natriuresis. Natriuresis and osmotic diuresis are transient but cause the effect of protecting the heart and kidneys. The multi-faceted effects of SGLT2i on serum magnesium and serum potassium caused
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GLP-1RAs enhance natriuresis by activating atrial cardiomyocytes to release ANP and reduce NHE3 activity. DPP-4i also possesses natriuretic effects, the mechanism of which is by increasing SDF-1α levels in addition to those mediated by GLP-1 levels. Insulin has a sodium-retaining effect and promotes the transfer of potassium, magnesium, and phosphate from extracellular to intracellular due to its physiological properties. The effects of diabetes and the use of hypoglycemic drugs on the water and electrolyte metabolism of patients are dual and complex. The paper provides clinicians with a comprehensive understanding of antidiabetic medications, an individualized and precise selection of medications, and targeted management of patients’ water and electrolyte levels. However, numerous factors affect water-electrolyte levels, and the same hypoglycemic agent may have different effects in patients. Thus, further research into the mechanisms by which hypoglycemic agents affect water-electrolyte metabolism is potentially beneficial in making more accurate judgments about patients’ conditions to avoid worse complications.

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Authors’ Contributions
Jian Zhang mainly wrote and revised the manuscript, and constructed the framework of the manuscript. Min-Min Han and Meng-Nan Li provided constructive opinions on the formation of the manuscript. Dan Yang, Gui-Mei Yang, and Xin-Tong Hou participated in the drawing of manuscript pictures and the investigation and sorting of documents. Yi Zhang and Yun-Feng Liu participated in the topic design, manuscript writing, manuscript editing, and providing instructional support. All authors contributed to the article and approved the submitted version.

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Conflict of Interest
The authors declare that there is no conflict of interest.

Data Availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Informed Consent
Not applicable.

Ethics Approval
Not applicable.

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