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REVIEW

Diabetes mellitus and electrolyte disorders

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Abstract

Diabetic patients frequently develop a constellation of electrolyte disorders. These disturbances are particularly common in decompensated diabetics, especially in the context of diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. These patients are markedly potassium-, magnesium- and phosphate-depleted. Diabetes mellitus (DM) is linked to both hypo- and hyper-natremia reflecting the coexistence of hyperglycemia-related mechanisms, which tend to change serum sodium to opposite directions. The most important causal factor of chronic hyperkalemia in diabetic individuals is the syndrome of hyporeninemic hypoaldosteronism. Impaired renal function, potassium-sparing drugs, hypertonicity and insulin deficiency are also involved in the development of hyperkalemia. This article provides an overview of the electrolyte disturbances occurring in DM and describes the underlying mechanisms. This insight should pave the way for pathophysiology-directed therapy, thus contributing to the avoidance of the several deleterious effects associated with electrolyte disorders and their treatment.

Key words: Glucose; Osmotic diuresis; Hyponatremia; Hyperkalemia; Hypomagnesemia

Core tip: Diabetic patients frequently develop a constellation of electrolyte disorders. These patients are often potassium-, magnesium- and phosphate-depleted, especially in the context of diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. Diabetes is linked to both hypo- and hyper-natremia, as well as to chronic hyperkalemia which may be due to hyporeninemic hypoaldosteronism. This article provides an overview of the electrolyte disturbances occurring in diabetes and describes the underlying mechanisms. This insight should pave the way for pathophysiology-directed therapy, thus contributing to the avoidance of the several deleterious effects associated with electrolyte disorders and their treatment.

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INTRODUCTION

Electrolyte disorders are common in clinical practice. They are mainly encountered in hospital populations occurring in a broad spectrum of patients (from asymptomatic to critically ill) and being associated with increased morbidity and mortality[1-3]. The disturbances of electrolyte homeostasis are also frequently observed in community subjects. Community-acquired electrolyte disorders, even chronic and mild, are related to poor prognosis[3]. Electrolyte disorders are usually multifactorial in nature. Various pathophysiological factors, such as nutritional status, gastrointestinal absorption capacity, coexistent acid-base abnormalities, pharmacological agents, other comorbid diseases (mainly renal disease) or acute illness, alone or in combination, play a key role.

Diabetes mellitus (DM) is included among the diseases with increased frequency of electrolyte abnormali-

Table 1 Principal causes of electrolyte disorders in diabetic patients

Sodium disorders[1]
Hyponatremia
Pseudohyponatremia (marked hyperlipidemia)
Hyperglycemia (hypertonicity)-induced movement of water out of the cells (dilutional hyponatremia)
Osmotic diuresis-induced hypovolemic hyponatremia
Drug-induced hyponatremia: hypoglycemic agents (chlorpropamide, tolbutamide, insulin) or other medications (*e.g.*, diuretics, amitriptyline)
Pseudonormonatremia (marked hyperlipidemia, severe hypoproteinemia)
Hypernatremia
Pseudohypernatremia (severe hypoproteinemia)
Loss of water in excess of sodium and potassium (osmotic dieresis), if this water loss is replaced insufficiently
Potassium disorders
Hypokalemia
Shift hypokalemia: insulin administration
Gastrointestinal loss of K^+: malabsorption syndromes (diabetic-induced motility disorders, bacterial overgrowth, chronic diarrheal states)
Renal loss of K^+: osmotic diuresis, hypomagnesemia, diuretics (thiazides, thiazide-like agents, furosemide)
Hyperkalemia
Shift hyperkalemia: acidosis, insulin deficiency, hypertonicity, rhabdomyolysis, drugs (*e.g.*, beta blockers)
Reduced glomerular filtration of K^+: acute and chronic kidney disease
Reduced tubular secretion of K^+: hyporeninemic hypoaldosteronism, drugs (angiotensin-converting enzyme inhibitors, angiotensin Ⅱ receptor blockers, renin inhibitors, beta blockers, potassium-sparing diuretics)
Magnesium disorders
Hypomagnesemia
Pseudohypomagnesemia: hypoalbuminemia
Shift hypomagnesemia: insulin administration
Poor dietary Mg^{2+} intake
Gastrointestinal Mg^{2+} losses: diarrhea as a result of diabetic autonomic neuropathy
Increased renal Mg^{2+} losses due to osmotic diuresis, glomerular hyperfiltration, diuretic administration
Recurrent metabolic acidosis
Calcium disorders
Hypocalcemia
Pseudohypocalcemia: hypoalbuminemia[2]
Acute renal failure due to accompanying hyperphosphatemia
Advanced chronic renal insufficiency due to hyperphosphatemia and low levels of vitamin D
Nephrotic syndrome: loss of 25-hydroxyvitamin D3 and its binding protein in the urine
Hypomagnesemia
Vitamin D deficiency
Drug-mediated: loop diuretics
Hypercalcemia
Concurrent hyperparathyroidism
Thiazide therapy
Phosphorus disorders
Hypophosphatemia
Osmotic diuresis
Drugs: thiazides, loop diuretics, insulin
Malabsorption syndromes
Primary hyperthyroidism
Vitamin D deficiency

[1]Spurious sodium disorders occur when sodium is measured with indirect ion-selective electrodes; [2]The ionized serum calcium levels are normal.

ties given that the aforementioned factors (especially impaired renal function, malabsorption syndromes, acid-base disorders and multidrug regimens) are often present in diabetics[4].

This article provides an overview of the electrolyte disturbances occurring in DM and describes possible underlying mechanisms (Table 1). This insight should pave the way for pathophysiology-directed therapy, possibly contributing to the avoidance of several deleterious effects associated with electrolyte disorders and their treatment.

DYSNATREMIAS (HYPONATREMIA AND HYPERNATREMIA)

DM is a well-known cause of dysnatremias *via* several underlying mechanisms[3,5]. Glucose is an osmotically active substance. Hyperglycemia increases serum osmolality, resulting in movement of water out of the cells and subsequently in a reduction of serum sodium levels ($[Na^+]$) by dilution. Therefore, in hyperglycemic patients, the corrected $[Na^+]$ should be taken into account, which is calculated by adding to measured $[Na^+]$ 1.6 mmol/L for every 100 mg/dL (5.55 mmol/L) increment of serum glucose above normal; a correction factor by 2.4 mmol/L is used when serum glucose concentrations are higher than 400 mg/dL (22.2 mmol/L)[6,7]. It is worth mentioning that the corrected $[Na^+]$ after adjustment for the dilutional effect of hyperglycemia should be considered as a useful tool for the monitoring of treatment in hyperglycemic states[8]. Uncontrolled DM can also induce hypovolemic-hypo-

natremia due to osmotic diuresis. Moreover, in diabetic ketoacidosis ketone bodies (b-hydroxybutyrate and acetoacetate) obligate urinary electrolyte losses and aggravate the renal sodium wasting[7,9]. It should be emphasized, however, that hypotonic renal losses (loss of water in excess of sodium and potassium) due to osmotic diuresis can lead to hypernatremia if this water loss is replaced insufficiently. In a study in 113 hypernatremic patients hospitalized in an internal medicine clinic, poorly controlled DM was implicated in the development of hypernatremia in one third of cases (34.5%)[5]. Consequently, in patients with uncontrolled DM serum concentration of [Na^+] is variable, reflecting the balance between the hyperglycemia-induced water movement out of the cells that lowers [Na^+], and the glucosuria-induced osmotic diuresis, which tends to raise [Na^+].

Drug-induced hyponatremia due to hypoglycemic agents (chlorpropamide, tolbutamide, insulin) or other medications (*e.g.*, diuretics, amitriptyline for the treatment of diabetic neuropathy) should be considered in every diabetic patient with low [Na^+][10,11]. Chlorpropamide, which is now rarely used in the treatment of patients with DM, can induce hyponatremia in approximately 4% to 6% by potentiating the effect of antidiuretic hormone. Elderly patients concomitantly using diuretics have greater risk of developing hyponatremia[12,13]. Tolbutamide can lead to hyponatremia by decreasing renal free water clearance[13]. Noteworthy, despite fluid retention being a common adverse effect of thiazolidinediones (pioglitazone and rosiglitazone), hyponatremia related to these drugs was reported only once[14]. There is experimental evidence that glucagon-like peptide 1 receptor agonists influence water and electrolyte balance[15]. However, to the best of our knowledge, dysnatremias (or other electrolyte disorders) related to these drugs have not reported in humans. Moreover, the new class of oral antidiabetic agents known as sodium-glucose cotransporter type 2 (SGLT2) inhibitors does not appear to be associated with electrolyte abnormalities in early clinical studies[16,17].

It has been reported that DM *per se* (independently of drugs or hyperglycemia) is associated with hyponatremia[11]. Recently, in a study in 5179 community subjects aged 55 years or more DM was associated with hyponatremia (OR = 1.98; 95%CI: 1.47-2.68), with the serum glucose levels being too low to fully explain the degree of hyponatremia[3]. Altered vasopressin metabolism, interaction between insulin and vasopressin, both of which act in the renal collecting duct, and the reabsorption of more hypotonic fluid due to slower stomach emptying have been proposed as possible underlying mechanisms of this association[18-20]. Although rare, the inverse etiological relation between hyponatremia and DM also exists. In fact, brain edema in the setting of untreated symptomatic hyponatremia may induce cerebral herniation and infarction of pituitary and hypothalamus, leading to central DM and insipidus[21].

DM is also associated with an artificially decreased or elevated serum sodium value, that is different compared with the actual systemic level. In normal subjects, serum is composed of water (approximately 93%), with fats and proteins accounting for the remaining 7%. Sodium is located in the serum water phase only. A reduction in serum water fraction (< 80%) may occur in patients with marked hyperlipidemia as with lactescent serum in uncontrolled DM. In these settings, the serum sodium concentration, measured per liter of serum, not serum water, is artificially reduced (pseudohyponatremia). The presence of normal serum sodium levels in a patient with hyperlipidemia should also raise the suspicion that hypernatremia may be present (pseudonormonatremia). The opposite phenomenon of pseudohypernatremia and pseudonormonatremia may also occur as a result of severe hypoproteinemia, not infrequently observed in diabetics with nephrotic or malabsorption syndromes. In lipemic or hypoproteinemic samples the direct ion-selective electrodes (ISE) method for the measurement of serum sodium should be used, since the indirect ISE is prone to spurious dysnatremias[22].

It is known that rapid correction of serum sodium may be followed by development of central demyelinating lesions, particularly in the pons (a disorder called central pontinemyelinolysis orosmotic demyelination) with major disability or even fatal outcome[2]. Diabetics may have an increased risk for the osmotic demyelination syndrome (ODS) during correction of hyponatremia since risk factors for this disorder (thiazide diuretics, malnutrition, hypokalemia, and hypoxia)[23] are not infrequently present in such patients. Hypokalemia is also associated with a poor outcome in patients who develop the syndrome[24].

It should be emphasized that ODS is mainly observed during overly rapid correction of chronic hyponatremia. However, in diabetic patients hypernatremia and hypokalemia (in the absence of hyponatremia or hyperosmolality) are rarely associated with ODS. The mechanism by which these electrolyte disorders may cause ODS in the diabetic state is not yet known[25,26].

It has been suggested that in cases of nonketotic hyperglycemic hyperosmolar syndrome (HHS) altered mental status is predicted best by [Na^+]; serum glucose concentration alone is considered a poor indicator. In fact, there is evidence that hyperglycemic patients with hypertonicity are symptomatic only if hypernatremia is present[5,27]. On the contrary, neurological symptoms may be absent in the context of severe gradually developing hyperglycemia[27,28]. This could be attributed to the capacity of the brain tissue to restore intracellular water by accumulating electrolytes and the so-called idiogenic osmoles. Furthermore, the brain cells are relatively permeable to glucose even in the absence of insulin[28,29]. Therefore, hyperglycemia by itself does not create severe hypertonicity in central nervous system (CNS)[28]. On the other hand, hypernatremia induces severe cellular dehydration in CNS cells. This state is associated with a rather slow compensatory accumulation of brain osmolar content[28].

The development of hypernatremia is associated with endocrine dysfunction. There is some evidence in

animals and man that hypernatremia and hyperosmolarity are associated with impairment of both insulin-mediated glucose metabolism and glucagon-dependent glucose release[30-33]. Thus, hypernatremia and hyperosmolarity should be considered as contributing factors to the occurrence of hyperglycemia in critically ill patients[34]. Moreover, hypernatremia is implicated in the profound inhibition of gonadotrophin release in postmenopausal diabetic women with HHS. Although the underlying mechanisms remain unknown, it appears that hypernatremia induces a decrease in gonadotrophin-releasing hormone expression in GT1-7 neurons[35].

Rhabdomyolysis, though uncommon, has been described in the diabetic state[36]. It appears that high serum sodium and glucose levels represent the most important determinants for the occurrence of this complication[37].

HYPOKALEMIA

The causes of hypokalemia in diabetics include: (1) redistribution of potassium [K^+] from the extracellular to the intracellular fluid compartment (shift hypokalemia due to insulin administration); (2) gastrointestinal loss of K^+ due to malabsorption syndromes (diabetic-induced motility disorders, bacterial overgrowth, chronic diarrheal states); and (3) renal loss of K^+ (due to osmotic diuresis and/or coexistent hypomagnesemia). Hypomagnesemia can cause hypokalemia possibly because a low intracellular magnesium [Mg^{2+}] concentration activates the renal outer medullary K^+ channel to secrete more K^+[38].

Exogenous insulin can induce mild hypokalemia because it promotes the entry of K^+ into skeletal muscles and hepatic cells by increasing the activity of the Na^+-K^+-ATPase pump[39]. The increased secretion of epinephrine due to insulin-induced hypoglycemia may also play a contributory role[40]. The major setting in which insulin administration leads to hypokalemia is during the treatment of severe hyperglycemia. The majority of patients with diabetic ketoacidosis (DKA) and HHS are markedly K^+-depleted. The average K^+ deficit is 3-5 mEq/kg, but it can exceed 10 mEq/kg in some cases[41,42]. A number of factors contribute to the DKA- and HHS-associated potassium depletion, including vomiting, increased renal losses due to the osmotic diuresis and ketoacid anion excretion, and the loss of K^+ from the cells due to glycogenolysis and proteolysis[41,43]. On admission, however, the serum K^+ levels are usually normal, or, in about one-third of patients, increased despite the K^+ depletion[41,43]. It is thought that hyperosmolality and insulin deficiency are primarily responsible for the relative rise in the serum potassium concentration in this setting. As mentioned, hyperglycemia increases serum osmolality resulting in movement of water out of cells. The loss of intracellular water leads to an increased intracellular K^+ concentration, favoring a gradient for K^+ to move out of the cells. Simultaneously, the friction forces between solvent (water) and solute can result in K^+ being carried along with water through the water pores in the cell membrane[43]. In contrast, acidemia probably does not play a major role given that organic acids are much less likely to influence the internal K^+ distribution[44]. Insulin therapy lowers K^+ concentration driving K^+ into cells (both directly and indirectly by reversing hyperglycemia). Therefore, insulin therapy may cause severe hypokalemia, particularly in patients with a normal or low serum K^+ concentration at presentation. Insulin administration in patients with massive K^+ deficits who are hypokalemic prior to therapy should be delayed until the serum K^+ is above 3.3 mEq/L to avoid possible arrhythmias, cardiac arrest and respiratory muscle weakness[42,45,46]. It is obvious that the risk of hypokalemia-related complications is particularly higher in diabetic subjects who have hypertension, myocardial infarction/ischemia, or heart failure as comorbidities. In addition, since diabetics are frequently on diuretics, diuretic-associated hypokalemia (as well as hypomagnesemia and hypophosphatemia) should be taken into account in this setting.

Hypokalemia is associated with impaired insulin secretion and decreased peripheral glucose utilization resulting in carbohydrate intolerance and hyperglycemia[47]. This is particularly problematic in diabetic patients causing a vicious circle where low serum K^+ levels lead to poorly controlled DM and vice versa.

HYPERKALEMIA

The incidence of hyperkalemia is higher in diabetic patients than in the general population[48,49]. Redistribution of potassium from the intracellular to the extracellular compartment (shift hyperkalemia) can induce hyperkalemia with no net total body K^+ increase. Examples of shift hyperkalemia in DM include acidosis (for each 0.1 fall in pH, potassium increases by approximately 0.4 mmol/L), insulin deficiency, hypertonicity, cell lysis (rhabdomyolysis), and drugs (*e.g.*, beta blockers). Reduced glomerular filtration of K^+ (due to acute kidney injury and chronic kidney disease) and many drugs that interfere with K^+ excretion are associated with hyperkalemia. These include angiotensin-converting enzyme inhibitors, angiotensin Ⅱ receptor blockers, renin inhibitors, beta blockers and potassium-sparing diuretics. Of note, the typical healthy diabetic diet is often rich in K^+ and low in sodium contributing to the occurrence of hyperkalemia in susceptible individuals[48,49]. Nevertheless, the most common causal factor of chronic hyperkalemia in diabetics is the reduced tubular secretion of K^+ due to the syndrome of hyporeninemic hypoaldosteronism[50]. This syndrome is characterized by mild to moderate renal insufficiency and patients typically present with asymptomatic hyperkalemia. The development of overt hyperkalemia is most common in patients with other risk factors that further impair the efficiency of potassium excretion, such as renal insufficiency, volume depletion, or the use of medications that interfere with potassium handling (see above).

Of note, dapagliflozin (a SGLT2 inhibitor) may be protective from the development of hyperkalemia in

patients with moderate renal impairment due to osmotic diuresis[17]. However, the administration of SGLT2 inhibitors in hypovolemic patients may cause elevated serum creatinine levels and decreases in glomerular filtration rate due to deterioration of intravascular volume contraction. Indeed, worsening renal function and hyperkalemia may occur in patients on canagliflozin, particularly those predisposed to hyperkalemia due to impaired renal function, medications or other medical conditions[51]. Hyporeninemic hypoaldosteronism is more frequently observed in diabetic and elderly patients as well as in those with chronic renal impairment. Diabetic nephropathy accounts for 43%-63% of cases comprising the most common cause of hyporeninemic hypoaldosteronism[33,50,52]. Normal ageing, especially after the sixth decade, is associated with a decline in renin production. Moreover, elderly patients may have decreased renal function even without significant elevations in serum creatinine levels [< 1.2 mg/dL (106 μmol/L)]. Consequently, diabetics (especially the elderly) on medications known to interfere with K^+ homeostasis are at increased risk for hyperkalemia[33,53]. In such cases, close K^+ monitoring is fully warranted[54]. Clinicians must also be alert that hyperkalemia in patients with type 1 DM may be due to concurrent adrenal insufficiency in the setting of autoimmune polyglandular syndrome[55].

HYPOMAGNESEMIA

Hypomagnesemia is a frequent electrolyte disorder in diabetic patients[56]. Recently, DM was identified as an independent risk factor for hypomagnesemia in community subjects aged 55 years or more (OR = 3.32; 95%CI: 2.00-5.50)[3]. In a recent prospective study in hypomagnesemic patients (either on admission or during hospitalization in an internal medicine clinic) DM was evident in a considerable proportion (40%), mainly as a contributing factor. Osmotic diuresis accompanied by inappropriate magnesiuria was the prominent underlying mechanism of hypomagnesemia in these diabetic patients[57]. Except for glucosuria, several other possible explanations for hypomagnesemia in DM have been reported. These include poor dietary intake, glomerular hyperfiltration, altered insulin metabolism, diuretic administration and recurrent metabolic acidosis[56]. Increased gastrointestinal Mg^{2+} losses due to diarrhea as a result of diabetic autonomic neuropathy can also cause low serum Mg^{2+} levels. Of note, a case of symptomatic hypomagnesemia [serum Mg^{2+} concentration 0.66 mEq/L (0.33 mmol/L), reference range 1.42-1.84 mEq/L (0.71-0.94 mmol/L)] was attributed to metformin-induced diarrhea[58]. Furthermore, insulin promotes net shift of Mg^{2+} from extracellular to intracellular space and can contribute to hypomagnesemia[59,60]. The increased secretion of epinephrine due to insulin-induced hypoglycemia may also play a role. The risk of hypomagnesemia related to insulin therapy is increased in poorly controlled diabetic patients given that hyperglycemia induces increased renal Mg^{2+} loss *via* osmotic diuresis. Hypokalemia, hypophosphatemia as well as acidosis-related urinary Mg^{2+} losses contribute to the high incidence of hypomagnesemia in the setting of diabetic ketoacidosis[61,62]. It should be noted that hypoalbuminemia is associated with spurious hypomagnesemia. In hypoalbuminemic states (serum albumin < 4 g/dL) the corrected serum Mg^{2+} should be calculated using the formula: corrected Mg^{2+} (mEq/L) = measured Mg^{2+}(mEq/L) + 0.01 × (40 - albumin in g/L)[63].

Mg^{2+} is essential for life being involved in numerous enzymatic reactions, including ATP use, cell membrane, ion channels and mitochondrial function, as well as protein synthesis. The most clinically significant consequences of hypomagnesemia are ascribed to alterations in the function of excitable membranes in nerve, muscle, and the cardiac conducting system. Moreover, low serum Mg^{2+} levels can secondarily induce hypokalemia, hypocalcemia, and hypophosphatemia, potentially causing further derangements in neuromuscular and cardiovascular physiology. Hypomagnesemia has been implicated in various long-term complications of DM, such as hypertension, increased carotid wall thickness, coronary artery disease, dyslipidemia, diabetic retinopathy, neuropathy, ischemic stroke, and foot ulcerations[56]. Hypomagnesemia has also been linked to diabetic nephropathy (from microalbuminuria to advanced renal disease)[64-66]. It has been proposed that hypomagnesemia is a predictor of end-stage renal disease in patients with diabetic nephropathy[66]. In addition, magnesium deficit is associated with carbohydrate intolerance and insulin resistance, thus inducing or worsening existing DM[67,68]. On the contrary, increased dietary Mg^{2+} intake has been associated with a reduced risk of type 2 DM[69].

HYPOCALCEMIA

Patients with DM have an increased risk for development of acute renal failure due to volume depletion, sepsis, rhabdomyolysis and drugs (*e.g.*, radiographic contrast media). In this setting severe hyperphosphatemia may occur when phosphorus cannot be excreted by the malfunctioning kidney either with or without increased cell catabolism, thus resulting in hypocalcemia. Advanced chronic renal insufficiency may be associated with hypocalcemia due to accompanying hyperphosphatemia and low levels of vitamin D. Patients with nephrotic syndrome may exhibit hypocalcemia, even if the glomerular filtration rate is well preserved. This is attributed to the loss of 25-hydroxyvitamin D_3 and its binding protein in the urine. Hypomagnesemia is another potential cause of hypocalcemia in diabetics. Mg^{2+} depletion leads to hypocalcemia mainly because of impaired release of parathyroid hormone (PTH) or skeletal and renal tubule resistance to the action of PTH[1]. Vitamin D deficiency and furosemide administration may also play a role in the occurrence of hypocalcemia[70]. There is evidence that diabetic patients are relatively hypoparathyroid[71]. In fact, a mild shift downwards in the set-point for PTH secretion in patients

with insulin-dependent DM as well as a diminished parathyroid gland responsiveness to hypocalcemia in uremic diabetic patients have been reported[72,73].

Hypoalbuminemia is associated with pseudohypocalcemia defined as a reduction of total serum calcium concentration in the presence of normal ionized serum calcium levels. In hypoalbuminemic states, one of the commonly used formulas to correct total calcium levels is by adding 0.8 mg/dL (0.2 mmol/L) to measured calcium values for every 1 g/dL decrease in serum albumin from normal value (assumed to be 4 g/dL). Given that the accuracy of this method is poor (particularly among critically ill and geriatric patients), the biologically active ionized calcium concentration should be measured when possible[1,74].

HYPERCALCEMIA

The incidence of DM in primary hyperparathyroidism and that of primary hyperparathyroidism in DM is approximately 8% and 1%, respectively. Both values are about three-fold higher than that anticipated in the general population[75]. Hyperparathyroidism is related to long-term insulin resistance and relative insulin insufficiency, leading to overt DM or deterioration of glycemic control of established DM[75,76]. It is thought that an elevated intracellular free calcium concentration (by decreasing normal insulin-stimulated glucose transport) increases the requirement for insulin, resulting in hyperparathyroidism-mediated insulin resistance[75]. Diabetic patients should be evaluated for hypercalcemia given that untreated hyperparathyroidism is linked to hypertension[75,77]. The detection of high serum calcium levels in a patient with type 1 DM should raise the suspicion that autoimmune hyperparathyroidism associated with anti-calcium-sensing receptor autoantibodies may be present[78]. Recently, a case of severe hypercalcemia [15 mg/dL (3.75 mmol/L)] in DKA was reported[79]. Dehydration might represent the most important causative factor for the occurrence of hypercalcemia in this case. A decreased bone formation due to metabolic acidosis and an increased bone mineral dissolution and resorption due to severe insulin deficiency and metabolic acidosis may also play a role[80]. Hyperglycemia-mediated inhibition of bone mineralization, insulin growth factor-1 deficiency, hypophosphatemia and immobilization are also included among the potential contributory factors of hypercalcemia in DKA[79,81,82]. Also, diabetic patients on thiazide diuretics are more prone to exhibit hypercalcemia.

HYPOPHOSPHATEMIA

Diabetic patients have underlying conditions that predispose to the development of hypophosphatemia. These include primary hyperthyroidism, vitamin D deficiency, malabsorption, and the use of diuretics (thiazides and furosemide)[83]. It is known that increased insulin levels promote the transport of both glucose and phosphate into the skeletal muscle and liver cells. However, in normal subjects the administration of insulin leads only to a slight decrement of serum phosphate levels. The risk of severe hypophosphatemia is increased in cases of underlying phosphate depletion[62,84]. Decompensated DM with ketoacidosisis associated with excessive phosphate loss due to osmotic diuresis. Despite phosphate depletion, the serum phosphate concentration at presentation is usually normal or even high because both insulin deficiency and metabolic acidosis cause a shift of phosphate out of cells[85]. Administration of insulin and fluids, and correction of ketoacidosis may reveal phosphate deficiency and cause a sharp decrease in plasma phosphate concentration due to intracellular shift[83].

In a study of 69 patient with DKA, the incidence of hyperphosphatemia was 94.7% at presentation. The mean serum phosphate concentration fell from 9.2 mg/dL (3 mmol/L) to 2.8 mg/dL (0.9 mmol/L) 12 h after initiating treatment, while some patients exhibited values as low as 1.0 mg/dL (0.32 mmol/L)[85].

The routine administration of phosphate during treatment of DKA and HHS is not recommended since randomized trials failed to show any clinical benefit from phosphate administration[42,83,86,87]. What is more, correction of hypophosphatemia may have adverse effects, such as hypocalcemia and hypomagnesemia[42,83,88]. Careful phosphate replacement is required in patients with severe hypophosphatemia of less than 1.0 mg/dL (0.32 mmol/L) and in patients who develop cardiac dysfunction, hemolytic anemia, or respiratory depression[42,89,90].

CONCLUSION

Electrolyte abnormalities are common in diabetic patients and may be associated with increased morbidity and mortality. These disturbances are particularly common in decompensated DM, in the elderly as well as in the presence of renal impairment. Patients with DM may receive complex drug regimens some of which may be associated with electrolyte disorders. Discontinuation of these medications, when possible, as well as strict control of glycemia are of paramount importance to prevent electrolyte abnormalities in diabetic patients. The successful management of these disorders can best be accomplished by elucidating the underlying pathophysiologic mechanisms.

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