REVIEW ARTICLE

ELECTROLYTE DISTURBANCES IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Diabetic patients frequently develop a constellation of electrolyte disorders. These derangement results from insulin deficiency, hyperglycemia and hyperketonemia. Hyperglycemia sets the internal environment for osmotic diuresis while causing a dilutional effect on electrolyte concentrations.The osmotic effect of glucose results in decreased circulating blood volume and fluid shift from the intracellular spaces causing cellular dehydration. These disturbances are particularly common in decompensated diabetes, especially in the context of diabetic ketoacidosis or non ketotic hyperglycemic hyperosmolar syndrome.These patients are markedly sodium, magnesium and phosphate depleted. Diabetes mellitus is linked to both hypo and hyperkalemia and also hypo and hypercalcemia reflecting coexistence of hyperglycemia related mechanisms, which tend to change serum potassium and calcium to opposite directions. This article provides an overview of the electrolyte disturbances occurring in Diabetes and mechanisms underlying those disturbances.

Key Words: Electrolyte disturbance, Diabetes mellitus, Diabetic ketoacidosis, Hyperglycemic hyperosmolar syndrome

Introduction

Electrolytes that are present in the human body play an important role in many body processes, such as controlling fluid levels, acid-base balance (pH), nerve conduction, blood clotting and muscle contraction. Potassium, sodium and calcium are all important for proper electrolyte balance. Electrolyte imbalance resulting from kidney failure, dehydration, fever, and vomiting has been suggested as one of the contributing factors toward complications observed in diabetes and other endocrine disorders[1]. Diabetes mellitus is a heterogeneous group of metabolic disorder characterized by high blood glucose level (hyperglycemia) with alteration in carbohydrate, lipid, and protein metabolism resulting from defects in insulin secretion and/or action. Diabetes mellitus (DM) is rapidly emerging as an important cause of mortality and morbidity in developing countries[2]. The number of persons affected by diabetes continues to increase worldwide. Estimates suggest that 438 million individuals will be affected in 2030[3] by diabetes. The prevalence of diabetes is of great concern worldwide and 20% to 50% of new onset type II diabetes mellitus is observed in young generation[4].

Diabetes Mellitus is an established risk factor for coronary heart disease (CHD), stroke, and end stage renal disease (ESRD). Diabetic nephropathy is one of the complications of diabetes mellitus, which ultimately leads to renal

failure and renal failure is a cause of electrolyte imbalance among hospitalized diabetic patients. Other causes are diarrhoea, vomiting, diuretic use and chronic laxative use[5]. Electrolyte imbalance is common in patients with diabetes, which could be the result of an altered distribution of electrolytes and it is related to hyperglycemia induced osmotic fluid shifts or of total-body deficits brought about by osmotic diuresis[4]. Complications from end organ injury and the therapies used in the management of diabetes may also contribute to electrolyte disturbances[6]. In diabetes mellitus, increased frequency of electrolyte abnormalities occur due to various pathophysiological factors such as nutritional status, gastrointestinal absorption capacity, co-existent of acid-base abnormalities, pharmacological agents, other comorbid diseases (mainly renal disease) or acute illness, alone or in combination, play a key role[7]. 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[8,9,10]. The disturbances of electrolyte homeostasis are also frequently observed in community subjects.

This article provides an overview of the electrolyte disturbances occurring in DM and describes possible underlying mechanisms. 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.

Sodium

Hyponatremia is the most common electrolyte abnormality in clinical practice and is associated with increased morbidity and mortality[11,12]. Even small decreases of serum sodium are associated with increased probability for adverse outcomes (cognitive impairment, falls, osteoporosis and fractures[13]. Decreased serum sodium levels are observed in diabetic patients due to numerous underlying pathogenetic mechanisms[7,14].

A) Non-hypotonic hyponatremia

With increased P_{osm}: Hyperglycemia - induced (dilutional)

With normal P_{osm}: Pseudohyponatremia (marked hypertriglyceridemia and

hyperproteinemia)

B) Hypotonic hyponatremia

- Hypovolemia-induced
- Drug -induced hyponatremia (mainly with thiazides and first generation sulphonylureas)
- Diabetes mellitus - associated hyponatremia
- Syndrome of inappropriate antidiuresis associated with coexisting disorders or administered drugs
- Chronic renal failure (diabetic nephropathy) or associated with the syndrome of hyporeninemic hypoaldosteronism

Increases in plasma glucose can lead to changes in plasma sodium concentrations through several mechanisms[6]. The direct measurement of serum osmolarity (P_{osm}) can differentiate between hypotonic hyponatremia (with decreased Psom) and hyponatremia associated with normal or even increased tonicity[15]. In fact, glucose is an osmotically active substance. Thus, in cases of marked hyperglycemia Psom is increased leading to movement of water out of cells and subsequently to a reduction of serum sodium levels (dilutional hyponatremia)[6]. In such cases the corrected, for the degree of hyperglycemia, sodium value should be calculated. Thus to obtain the "true" sodium levels in cases of extreme hyperglycemia, the addition of 2.4 mEq/L to the measured concentration for every 100 mg/dl increment in plasma glucose of above normal levels is required[16]. This corrected sodium level should be used during treatment of severe hyperglycemic states[17]. In patients with

dilutional hyponatremia the treatment of hyperglycemia is usually followed by a normalization of serum sodium levels[14]. Hyponatremia can also develop if a patient with uncontrolled diabetes has marked hypertriglyceridemia, even when the sodium concentration in plasma water is normal: a phenomenon called pseudohyponatremia[18]. Diagnosis of pseudohyponatremia is necessary to avoid dangerous overtreatment. It should be mentioned that, this case does not produce any of the symptoms classically attributed to hyponatremia. Improvement in glycemic control is associated with a rapid decrease in serum triglycerides resulting in the correction of pseudohyponatremia, thus no treatment is required[14]. The most common cause of hypotonic hyponatremia in patients with diabetes is osmotic diuresis-induced hypovolemia[4]. The patients with diabetic ketoacidosis, the excretion of β-hydroxybutyrate and acetoacetate obligate urine sodium resulting in aggravation of hypovolemia[19]. Drugs are common causes of hyponatremia in individuals with diabetes[20]. A number of drugs (mainly thiazides, in combination with SSRIs[21]), the first generation sulfonylureas (such as tolbutamide and chlorpropamide)[14,21], NSAIDs, angiotensin converting enzyme inhibitors, rosiglitazone or even amlodipine[20]. Patients with central nervous system disorders, pulmonary disorders including lung infections, and malignancies may exhibit hyponatremia due to the syndrome of inappropriate antidiuresis[14,15,21-23]. Patients with diabetic nephropathy and chronic renal failure are very prone to the development of hyponatremia due to decreased water excretion. Additionally, diabetic patients with hyporeninemic hypoaldosteronism commonly exhibit exaggerated natriuresis leading to volume depletion induced increase in ADH secretion, decreased water excretion and mild hyponatremia associated with asymptomatic hyperkalemia, and hyperchloremic metabolic acidosis[24]. It has been suggested that the altered vasopressin regulation in diabetes mellitus, the increased insulin induced potentiation of vasopressin-induced aquaporin AQP-2 water channels expression and the absorption of water from the GI tract due to slower stomach emptying may play a role in the association between diabetes mellitus and decreased serum sodium levels[25,26]. Taking into consideration the multifactorial origin of hyponatremia in most patients with diabetes a cause-specific treatment is required. Administration of insulin drives glucose and water into the cells, reverses the initial direction of water movement and results in an increment of serum sodium levels.

Potassium

The causes of hypokalemia in diabetes 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 (diabetes-induced motility disorders, bacterial overgrowth, chronic diarrheal states); and (3) renal loss of K^+ (due to osmotic diuresis and/or co-existent hypomagnesemia). Hypomagnesemia can cause hypokalemia possibly because a low intracellular Mg^{2+} concentration activates the renal outer medullary K^+ channel to secrete it more[27]. Hypokalemia is associated with impaired insulin secretion and decreased peripheral glucose utilization resulting in carbohydrate intolerance and hyperglycemia[28]. 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[29]. The increased secretion of epinephrine due to insulin-induced hypoglycemia may also play a contributory role[30]. 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[31,32]. 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[31,33]. 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[33]. Insulin therapy lowers K^+ concentration driving K^+ into cells (both directly and indirectly by reversing hyperglycemia). 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 diabetic patients are frequently on diuretics, diuretic-associated hypokalemia (as well as hypomagnesemia and hypophosphatemia) should be taken into account in this setting[14].

Hyperkalemia can be caused by an increase in plasma tonicity that results from the redistribution of potassium from the intracellular space to the extracellular space[34]. In patients with type 2 diabetes, the insulin-mediated uptake of glucose is impaired, but the cellular uptake of potassium remains normal, a situation that is consistent with the divergence of intracellular pathways that follows activation of the insulin receptor[35]. The efflux of potassium from the cell is due to intracellular dehydration, which results from the osmotically induced, transcellular movement of water. This movement creates a favorable gradient for the efflux of potassium[36]. 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 (eg,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. Nevertheless, the most common causal factor of chronic hyperkalemia in diabetes is the reduced tubular secretion of K^+ due to the syndrome of hyporeninemic hypoaldosteronism[24]. Consequently, diabetic patients (especially the elderly) on medications known to interfere with K^+ homeostasis are at increased risk for hyperkalemia[37,38]. In such cases, close K^+ monitoring is fully warranted[39].

Calcium

Hypocalcemia is a potential complication of diabetic nephropathy in patients with the nephrotic syndrome, even if the glomerular filtration rate is well preserved.The nephrotic state leads to urinary loss of 25-hydroxyvitamin D3 and its carrier protein[40]. Alterations in the set point for parathyroid hormone release and circulating levels in patients with diabetes are reminiscent of those found in hypoparathyroidism, having the potential to exacerbate the tendency for the development of hypocalcemia[41,42]. Hypomagnesemia can be a cause of hypocalcemia because magnesium deficiency can result in impaired release of and or skeletal and renal tubule resistance to the action of parathyroid hormone[43]. Vitamin D deficiency and frusemide administration may also play a role in the occurrence of hypocalcemia[44]. Patients with DM have an increased risk for development of acute renal failure due to volume depletion, sepsis, rhabdomyolysis and drugs (eg 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[14]. Primary hyperparathyroidism should be considered in patients with diabetes who have

hypercalcemia[45]. It also found in patients with volume depletion, which leads to the increased reabsorption of renal calcium[46]. Hyperparathyroidism is related to long-term insulin resistance and relative insulin insufficiency, leading to overt DM or deterioration of glycemic control of established DM[47,48]. It is thought that an elevated intracellular free calcium concentration increases the requirement for insulin, resulting in hyperparathyroidism-mediated insulin resistance[47]. Diabetes patients should be evaluated for hypercalcemia given that untreated hyperparathyroidism is linked to hypertension[47,49]. 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[50].

Magnesium

Magnesium is an essential ion for human health, as it is involved in virtually every mechanism in the cell, including energy homeostasis, protein synthesis and DNA stability[51]. Hypomagnesemia is a frequent electrolyte disorder in diabetic patients[52]. In addition, hypomagnesemia may impair glucose disposal and contribute to cardiovascular disease, retinopathy, and nephropathy[53]. The incidence of hypomagnesemia in patients with type 2 diabetes ranges widely, from 13.5% to 47.7%. These include poor dietary intake, glomerular hyperfiltration, altered insulin metabolism, diuretic administration and recurrent metabolic acidosis[52]. Furthermore, insulin promotes net shift of Mg^{2+} from extracellular to intracellular space and can contribute to hypomagnesemia[54,55]. Proton-pump inhibitors impair the gastrointestinal absorption of magnesium[56]. In patients with diabetic ketoacidosis, the osmotic diuresis resulting from poor glycemic control may lead to renal magnesium wasting. However the administration of insulin and the correction of acidosis shift magnesium into cells, and increased adrenergic activity may contribute to intracellular shifts in magnesium[57]. 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[52]. Hypomagnesemia has also been linked to diabetic nephropathy (from microalbuminuria to advanced renal disease)[58,59,60]. It has been proposed that hypomagnesemia is a predictor of end-stage renal disease in patients with diabetic nephropathy[60,61].

Phosphate

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)[62]. 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[63,64]. Decompensated DM with ketoacidosis 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[65]. Administration of insulin and fluids, and correction of ketoacisosis may reveal phosphate deficiency and cause a sharp decrease in plasma phosphate concentration due to intracellular shift[62]. Correction of hypophosphatemia may have adverse effects, such as hypocalcemia and hypomagnesemia[32,62,66]. 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[32,67,68].

Conclusion

Electrolyte abnormalities are common in diabetes patients and may be associated with increased morbidity and mortality. Electrolyte imbalance has a significant effect upon the risk of contracting many diseases. These disturbances are particularly common in decompensated diabetes, in the elderly as well as in the presence of renal impairment. Patients with diabetes mellitus 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. Also early diagnosis, good glycemic control and dietary modification are usually enough for prevention and treating complications in diabetes mellitus.

References

1. Husain F, Arifmaan M, Sheikh MA, Nawaz H, Jamil A. Trace elements status in type 2 Diabetes. **Bangladesh J Med Sci** 2009; **8:** 52-56.

2. Zaman MM, Chowdhury SR, Ahmed J, Numan SM, Islam SM and Yoshiike N. Non biochemical risk factors for cardiovascular disease in general clinic-based rural population of Bangladesh. **J Epidemiol** 2004; **14:** 63-68.

3. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of Diabetes for 2010 and 2030. **Diabet Res Clin Pract** 2010; **87(1):** 4-14.

4. Datchinamoorthi S, Vanaja R, Rajagopalan B. Evaluation of serum electrolytes in type II diabetes Mellitus. **Int J Pharm Sci Rev Res** 2016; **40(1):** 251-253.

5. Haque HF, Amin MG, Uddin KN, Ahmed JU, Ahmed AKMS, Rahim MA, Dewan P, Samad T. Pattern of electrolyte imbalance in Hospitalized Diabetic Patients; Experience in a tertiary Care Hospital. **Birdem Med J** 2012; **2(1):** 14-18.

6. Palmer BF and Clegg DJ. Electrolyte and acid-base disturbances in patients with Diabetes mellitus. **N Engl J Med** 2015; **373:** 548-559.

7. Elisaf MS, Tsatsoulis AA, Katopodis KP, Siamopoulos KC. Acid-base and electrolyte disturbances in patients with diabetic ketoacidosis. **Diabetes Res Clin Pract** 1996; **34:** 23-27.

8. Liamis G, Kalogirou M, Saugos V, Elisaf M. Therapeutic approach in patients with dysnatremias. **Nephrol Dial Transplant** 2006; **21:** 1564-1569.

9. Liamis G, Milionis HJ, Elisaf M. A review of drug induced hypocalcemia. **J Bone Miner Metab** 2009; **27:** 635-642.

10. Liamis G, Rodenburg EM, Hofman A, Zietse R, Striker BH, Hoom EJ. Electrolyte disorders in community subjects: prevalence

and risk factors. **Am J Med** 2013; **126:** 256-263.

11. Walker SS, Mount DM, Curhan GC. Mortality after hospitalization with mild, moderate and severe hyponatremia. **Am J Med** 2009; **122:** 857-865.
12. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH. Electrolyte disorders in community subjects: prevalence and risk factors. **Am J Med** 2013; **126:** 256-263.
13. Podesta MA, Faravelli I, Cucchiari D, Reggiani F, Oldani. Neurological counterparts of hyponatremia: pathological mechanisms and clinical manifestations. **Curr Neurol Neurosci Rep** 2015; **15:** 18.
14. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. **World J Clin Cases** 2014; **2:** 488-496.
15. Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. **CMAJ** 2012; **166:** 1056-1062.
16. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. **Am J Med** 1999; **106:** 399-403.
17. Liamis G, Gianoutsos C, Elisaf MS. Hyperosmolar nonketotic syndrome with hypernatremia: how can we monitor treatment? **Diabet Metab** 2009; **26:** 403-405.
18. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. **Am J Nephrol** 2013; **38:** 50-57.
19. Chiasson JL, Aris-Jilwan N,Belanger R. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. **CMAJ** 2003; **168:** 859-866.
20. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. **Am J Kidney Dis** 2008; **52:** 144-153.
21. Blijderveen JC, Straus SM, Rodenburg EM, Zietse R, Stricker BH et al.Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide. **Am J Med** 2014; **127:** 763-771.
22. Liamis G, Milionis HJ, Elisaf M. Hyponatremia in patients with infectious diseases. **J Infect** 2011; **63:** 327-335.
23. Liamis G, Milionis HJ, Elisaf M. Endocrine disorders; causes of hyponatremia not to neglect. **Ann Med** 2011; **43:** 179-187.
24. Defronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. **Kidney Int** 1980; **17:** 118-134.
25. Bankir L, Bardoux NP, Ahloulay M.Vasopressin and diabetes mellitus. **Nephron** 2001; **87:** 8-18.
26. Bustamante M, Hasler U, Kotova O, Chibalin AV, Mordasini D. Insulin potentiates AVP-induced AQP2 expression in cultured renal collecting duct principal cells. **Am J Physiol Renal Physiol** 2005; **288:** 334-344.
27. Yang L, Frindt G, Palmer LG. Magnesium modulates ROMK channel-mediated potassium secretion. **J Am Soc Nephrol** 2010; **21:** 2109-2116.
28. Wilcox CS. Metabolic and adverse effects of diuretics. **Semin Nephrol** 1999; **19:** 557-568.
29. Minaker KL and Rowe JW. Potassium homeostasis during hyperinsulinemia: effect of insulin level, beta-blockade, and age. **Am J Physiol** 1982; **242:** 373-377.
30. Petersen KG, Schlüter KJ, Kerp L. Regulation of serum potassium during insulin-induced hypoglycemia. **Diabetes** 1982; **31:** 615-617.
31. Kreisberg RA. Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment. **Ann Intern Med** 1978; **88:** 681-695.
32. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. **Diabetes Care** 2006; **29:** 2739-2748.

33. Adrogue HJ, Lederer ED, Suki WN, Eknoyan G. Determinants of plasma potassium levels in diabetic ketoacidosis. **Medicine (Baltimore)** 1986; **65:** 163-172.

34. Palmer BF. A physiologic-based approach to the evaluation of a patient with hyperkalemia. **Am J Kidney Dis** 2010; **56:** 387-393.

35. Nguyen TQ, Maalouf NM, Sakhaee K, Moe OW. Comparison of insulin action on glucose versus potassium uptake in humans. **Clin J Am Soc Nephrol** 2011; **6:** 1533-1539.

36. Tzamaloukas AH, Ing TS, Elisaf MS. Abnormalities of serum potassium concentration in dialysis-associated hyperglycemia and their correction with insulin: a unique clinical/physiologic exercise in internal potassium balance. **Int Urol Nephrol** 2010; **42:** 1015-1022.

37. Liamis G, Milionis H, Elisaf M. Blood pressure drug therapy and electrolyte disturbances. **Int J Clin Pract** 2008; **62:** 1572-1580.

38. Oxlund CS, Henriksen JE, Tarnow L, Schousboe K, Gram J, Jacobsen IA. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. **J Hypertens** 2013; **31:** 2094-2102.

39. Raebel MA, Ross C, Xu S, Roblin DW, Cheetham C, Blanchette CM, Saylor G, Smith DH. Diabetes and drug-associated hyperkalemia: effect of potassium monitoring. **J Gen Intern Med** 2010; **25:** 326-333.

40. Goldstein DA, Haldimann B, Sherman D, Norman AW, Massry SG. Vitamin D metabolites and calcium metabolism in patients with nephrotic syndrome and normal renal function. **J Clin Endocrinol Metab** 1981; **52:** 116-121

41. Mcnair P, Christensen MS, Madsbad S, Christiansen C, Transbol I. Hypoparathyroidism in diabetes mellitus. **Acta Endocrinol** 1981; **96:** 81-86.

42. Schwarz P, Sørensen HA, Momsen G, Friis T, Transbol I, Mcnair P. Hypocalcemia and parathyroid hormone responsiveness in diabetes mellitus: a tri-sodium-citrate clamp study. **Acta Endocrinol** 1992; **126:** 260-263.

43. Liamis G, Milionis HJ, Elisaf M. A review of drug induced hypocalcemia. **J Bone Miner Metab** 2009; **27:** 635-642.

44. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. **Endocrinol Metab Clin North Am** 2010; **39:** 419-446.

45. Taylor WH, Khaleeli AA. Coincident diabetes mellitus and primary hyperparathyroidism. **Diabet Metab Res Rev** 2001; **17:** 175-180.

46. Palmer BF. Metabolic complications associated with use of diuretics. **Semin Nephrol** 2011; **31:** 542-552.

47. Taylor WH, Khaleeli AA. Coincident diabetes mellitus and primary hyperparathyroidism. **Diabet Metab Res Rev** 2005; **17:** 175-180.

48. Procopio M, Borretta G. Derangement of glucose metabolism in hyperparathyroidism. **J Endocrinol Invest** 2003; **26:** 1136-1142.

49. Gulcelik NE, Bozkurt F, Tezel GG, Kaynaroglu V, Erbas T. Normal parathyroid hormone levels in a diabetic patient with parathyroid adenoma. **Endocrine** 2009; **35:** 147-150.

50. Topaloglu AK, Yildizdas D, Yilmaz HL, Mungan NO, Yuksel B, Ozer G. Bone calcium changes during diabetic ketoacidosis: a comparison with lactic acidosis due to volume depletion. **Bone** 2005; **37:** 122-127.

51. Debaaij JHF, Hoenderop JGJ, Bindels RJM.Magnesium in man: implications for health and disease. **Physiol Rev** 2015; **95:** 1-46.

52. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. **Clin J Am Soc Nephrol** 2007; **2:** 366-373.

53. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. **Arch Biochem Biophys** 2007; **458:** 40-47.

54. Paolisso G, Sgambato S, Passariello N, Giugliano D, Scheen A, D'Onofrio F, Lefèbvre PJ. Insulin induces opposite changes in plasma and erythrocyte magnesium concentrations in normal man. **Diabetologia** 1986; **29:** 644-647.

55. Matsumura M, Nakashima A, Tofuku Y. Electrolyte disorders following massive insulin overdose in a patient with type 2 diabetes. **Intern Med** 2000; **39:** 55-57.

56. Perazella MA. Proton pump inhibitors and hypomagnesemia: a rare but serious complication. **Kidney Int** 2013; **83:** 553-556

57. Romani AM. Cellular magnesium homeostasis. **Arch Biochem Biophys** 2011; **512:** 1-23.

58. Corsonello A, Ientile R, Buemi M, Cucinotta D, Mauro VN, Macaione S, Corica F. Serum ionized magnesium levels in type 2 diabetic patients with microalbuminuria or clinical proteinuria. **Am J Nephrol** 2000; **20:** 187-192.

59. Pham PC, Pham PM, Pham PA, Pham SV, Pham HV, Miller JM, Yanagawa N, Pham PT. Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. **Clin Nephrol** 2005; **63:** 429-436.

60. Sakaguchi Y, Shoji T, Hayashi T, Suzuki A, Shimizu M, Mitsumoto K, Kawabata H, Niihata K, Okada N, Isaka Y, et al. Hypomagnesemia in type 2 diabetic nephropathy: a novel predictor of end-stage renal disease. **Diabetes Care** 2012; **35:** 1591-1597.

61. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. **Arch Biochem Biophys** 2007; **458:** 40-47.

62. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. **J Clin Endocrinol Metab** 1983; **57:** 177-180.

63. Liamis G, Milionis HJ, Elisaf M. Medication induced hypophosphatemia: a review. **QJM** 2010; **103:** 449-459.

64. Moe SM. Disorders involving calcium, phosphorus, and magnesium. **Prim Care** 2008; **35:** 215-237, v-vi.

65. Kebler R, Mcdonald FD, Cadnapaphornchai P. Dynamic changes in serum phosphorus levels in diabetic ketoacidosis. **Am J Med** 1985; **79:** 571-576.

66. Winter RJ, Harris CJ, Phillips LS, Green OC. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. **Am J Med** 1979; **67:** 897-900.

67. Kreisberg RA. Phosphorus deficiency and hypophosphatemia. **Hosp Pract** 1977; **12:** 121-128.

68. Evans KJ, Thompson J, Spratt SE, Lien LF, Vorderstrasse A. The implementation and evaluation of an evidence-based protocol to treat diabetic ketoacidosis: a quality improvement study. **Adv Emerg Nurs J** 2014; **36:** 189-198.