Editorial Comment

Insulin for the treatment of hyperkalemia: a double-edged sword?

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Potassium plays a critical role in cellular metabolism and normal neuromuscular function. Tightly regulated homeostatic mechanisms have developed in the process of evolution to provide primary defense against the threats of hyper- and hypokalemia. The kidney plays a primary role in potassium balance, by increasing or decreasing the rate of potassium excretion. Distribution of potassium between the intracellular and the extracellular fluid compartments is regulated by physiologic factors such as insulin and catecholamines which stimulate the activity of the Na^+/K^+ ATPase. Only about 10% of the ingested potassium is excreted via the gut under normal physiologic conditions [1].

End stage renal disease (ESRD) patients rely largely on extra-renal mechanisms and dialysis to maintain potassium homeostasis. Despite the availability of dialysis and the adaptive increase in colonic excretion of potassium in renal insufficiency, severe hyperkalemia (defined as serum potassium level $> 6 \text{ mEq/L}$ [6 mmol/L]) is observed in 5–10% of maintenance dialysis patients and is responsible for 0.7% of deaths in the dialysis population in the United States [2–4]. Several factors can explain the high incidence of hyperkalemia in this population. Tolerance for a rapid potassium load is impaired in ESRD, not only because of lack of renal excretion, but also as a result of impaired cellular distribution of potassium [5]. The latter may result from defect in the Na^+/K^+ ATPase and possibly elevated glucagon levels in uremia [5, 6]. High dietary potassium intake and missed dialysis treatments are common contributors to hyperkalemia in ESRD patients. Other factors such as constipation (decreased colonic excretion) and fasting state (relative lack of insulin) may also predispose ESRD patients to hyperkalemia [7]. Patients who are new to dialysis may still have some residual renal function and remain sensitive to several classes of medications that impair potassium excretion. These include inhibitors of the renin-angiotensin-aldosterone system (RAAS), potassium sparing diuretics, heparin, trimethoprim, pentamidine and non-steroidal anti-inflammatory medications (NSAIDs). Use of spironolactone in prevalent ESRD patients has also been implicated as a cause for hyperkalemia due to its effect on colonic handling of potassium. Non-selective beta blockers can also lead to hyperkalemia by preventing intracellular shifts of potassium [8].

The treatment of acute hyperkalemia in ESRD patients is emergent dialysis. When dialysis is not immediately available, temporizing measures are employed. Intravenous calcium is used to counter the adverse myocardial effects of

hyperkalemia but does not affect the serum concentration of potassium. Cation exchange resins are frequently used to increase colonic secretion of potassium. However, due to their late onset of action (at least two hours), questionable efficacy, and possible toxicities such as colonic necrosis, cation exchange resins are not the recommended first-line therapy in acute hyperkalemia [9]. The use of intravenous bicarbonate therapy has also been discouraged due to the lack of benefit [10, 11]. Other measures that result in the shift of potassium from the extracellular to intracellular space, such as albuterol and insulin, have been proven to be effective in patients with chronic kidney disease (CKD) and are more rapid in onset, usually over 30–60 minutes [2, 12–14]. However, for unclear reasons, a subset of ESRD patients is resistant to the actions of albuterol [8]. Intravenous (IV) insulin is therefore often the first-line therapy for acute hyperkalemia in hospitalized ESRD patients. It is typically used in conjunction with dextrose to prevent hypoglycemia, and is often combined with other therapies such as nebulized albuterol.

Even though insulin-mediated glucose uptake is impaired in uremia, the potassium-lowering effect of insulin is unaffected [7]. This is thought to be due to the independent pathways for potassium and glucose transport across cell membrane [15]. Insulin shifts potassium into cells by stimulating the activity of Na^+/H^+ antiporter on cell membrane, promoting the entry of sodium into cells, which leads to activation of the Na^+/K^+ ATPase, causing an electrogenic influx of potassium. IV insulin leads to a dose-dependent decline in serum potassium levels [16]. A combination of IV insulin dose of 10 units plus 25 g of dextrose reliably lowers the serum potassium level by 1 mEq/L (mmol/L) within 10–20 minutes and the effect lasts about 4–6 hours [17, 18]. However, this therapy may be associated with significant hypoglycemia [14, 18–21]. In one study of hospitalized patients treated with IV insulin for hyperkalemia, 8.7% of the patients developed hypoglycemia (defined as blood glucose of $< 70 \text{ mg/dL}$ [3.9 mmol/L]) [20]. In a study of hemodialysis patients, 75% of patients treated with insulin and glucose to lower serum potassium level developed hypoglycemia [14].

The definition of hypoglycemia has been a topic of debate. The workgroup of the American Diabetes Association and the Endocrine Society defines iatrogenic hypoglycemia in patients with diabetes mellitus (DM) as “all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm.”

A plasma glucose concentration of ≤ 70 mg/dL [3.9 mmol/L] is recommended as the alert value even though symptoms of hypoglycemia usually develop at a level below this threshold [22, 23]. This value allows time for close monitoring of the patient to prevent symptomatic hypoglycemia and has been used to define hypoglycemia in numerous clinical trials.

Hypoglycemia in the inpatient setting is a common problem, with incidences ranging from 3.5% to 10.5% on the general medicine wards, 23% in surgical patients, and 10% in the ICU [24]. The symptoms of hypoglycemia can include irritability, impaired cognitive function, seizures, coma, ventricular arrhythmias, and even death [22, 24, 25]. There are multiple risk factors for hypoglycemia. These include medications, drug-to-drug interaction, endogenous insulin deficiency (with concomitant abnormal glucagon response), critical illness, poor nutritional intake, low body weight, older age, history of recurrent hypoglycemia, liver failure, and renal failure [20, 23, 24].

In this issue of Clinical Kidney Journal, Apel *et al* [26] reports the incidence and timing of hypoglycemia, as well as associated risk factors in 221 inpatient ESRD patients after treatment of hyperkalemia with 10 units of IV insulin and 25 g of dextrose. In this uncontrolled, retrospective study, Apel *et al* found a 13% incidence of hypoglycemia (defined as blood glucose < 60 mg/dL [3.33 mmol/L]). Of the patients who developed hypoglycemia, 66% did not have a history of DM and this was statistically significant, when compared to those that did not develop hypoglycemia. Also, patients who developed hypoglycemia had a lower body mass index (26 vs 29), although this did not reach statistical significance ($p = 0.06$). Risk factors for hypoglycemia were: no prior diagnosis of DM, no use of DM medication prior to admission, and a lower pre-treatment glucose level. Hypoglycemia occurred at a median of 2 hours after insulin and persisted for a median of 2 hours.

Patients with CKD and ESRD are particularly at risk for hypoglycemia [27, 28]. In the setting of normal kidney function, the kidney contributes to nearly half of overall gluconeogenesis, and is therefore as important as the liver in carbohydrate metabolism [29, 30]. The kidney also plays a critical role in insulin metabolism. Even though evidence implies that CKD creates an insulin-resistant state, hypoglycemia can ensue due to decreased gluconeogenesis and insulin degradation [31]. Other factors such as altered drug metabolism, malnutrition, decreased hepatic gluconeogenesis, and infection also increase the risk of hypoglycemia in this population [27, 32]. In hemodialysis patients, the use of glucose-free dialysis solution increases the risk of hypoglycemia due to transfer of plasma glucose to the dialyzate. Addition of glucose to dialysis solution significantly decreases this risk [33, 34]. Apel *et al* do not specify in their study whether there is a difference between hemodialysis and peritoneal dialysis patients. Theoretically, the incidence of hypoglycemia is lower in peritoneal dialysis due to the presence of dextrose in the dialysis solution.

The results from Apel's study emphasize the importance of intense blood glucose monitoring after insulin administration. Apel's study defined hypoglycemia as ≤ 60 mg/dL [3.33 mmol/L] and even with this conservative definition, the incidence was 13%. Since IV insulin is a commonly used therapy for severe hyperkalemia in ESRD patients in the hospital setting, we agree with Apel *et al* that a protocol-driven approach may be able to decrease the incidence of hypoglycemia. Published literature indicates

that the insulin and dextrose regimen varies from center to center. Dose of insulin ranges from 5–10 units and amount of glucose ranges from 25 to 60 g [35]. Others have recommended additional dextrose infusion after intravenous push of dextrose and insulin to prevent hypoglycemia [17, 20]. Due to risks of hypoglycemia, some have advocated the use of glucose alone in the treatment of hyperkalemia. The rationale is based on the theory that exogenous glucose stimulates insulin secretion which shifts potassium into the cell. In a randomized, crossover study of 10 non-diabetic, ESRD patients on hemodialysis with hyperkalemia, dextrose alone led to a clinically significant decrease in serum potassium level. The rates of hyperglycemia were not reported [36]. However, some concerns have been raised regarding this approach. Endogenous insulin secretion may be unpredictable, especially in the acutely ill and in those with insulin deficiency [8, 36]. The resultant hyperglycemia raises the plasma osmolality, which leads to movement of potassium out of the cell, worsening hyperkalemia. Conversely, some have suggested the use of insulin alone in the setting of hyperglycemia, but this is not widely accepted or practiced due to the high likelihood of inducing hypoglycemia [7, 18].

Similar to the current study, Shafers *et al* also noted that the majority (74%) of patients who developed hypoglycemia did not have a diagnosis of DM at the time of treatment for hyperkalemia [20]. This is an important point since patients without DM are at risk for lack of monitoring of their blood glucose levels. Hospital staff are trained to monitor blood glucose in patients with DM and the absence of this diagnosis makes the patient more vulnerable. Also, patients without DM have greater insulin sensitivity and are more prone to develop hypoglycemia after insulin administration.

The protocol proposed by Apel *et al* in this study for glucose monitoring and dextrose support in the treatment of hyperkalemia with IV insulin is designed to prevent hypoglycemia. We agree that the risk of hypoglycemia can be minimized by increasing the dextrose dose. However, there may be a risk for hyperglycemia if 25 g of dextrose is given 1 hour after insulin/dextrose administration 'irrespective of blood glucose level.' Based on experience at our institution and recommendations by experts, we contend that a baseline blood glucose level of ≥ 250 mg/dL will not require additional doses of intravenous dextrose, after the initial 25 g. However, this recommendation has not been validated in clinical studies.

At our center, the patient's body weight is taken into account before insulin and dextrose are administered. The protocol at our center is to administer 25 g of dextrose with IV insulin 0.1 units/kg of body weight. This regimen is followed by 250 mL of D10W infused over 2 hours. The use of a weight based insulin regimen reduces the risk of hypoglycemia in individuals with low body mass index, especially the elderly. Limited data have suggested that the administration of dextrose before insulin is effective and safe [37]. At our center, dextrose is given immediately prior to IV insulin. Blood glucose levels are obtained at baseline, 1, 2 and 3 hours post treatment. Since the implementation of this protocol, the incidence of hypoglycemia in hospitalized patients at our center has increased from approximately 20% to less than 5%.

As stated previously, beta-agonists, such as inhaled albuterol, have additive potassium-lowering effect due to a different mechanism of action. Beta-agonists, when used with insulin, may have the additional benefit of reducing

the risk of hypoglycemia since they promote gluconeogenesis in the liver [14, 38].

In conclusion, ESRD patients are at high risk of developing severe, life-threatening hyperkalemia. When dialysis is not immediately available, non-dialytic therapies are used as temporizing measures. Treatment with insulin is effective, but can be associated with severe hypoglycemia if appropriate therapeutic guidelines are not implemented and practiced. Education of physicians and nursing personnel, and adherence to an institution-specific treatment algorithm for hyperkalemia are extremely important in preventing this critical iatrogenic complication.

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References

- Sorensen MV, Matos JE, Praetorius HA et al. Colonic potassium handling. *Pflugers Arch* 2010; 459(5): 645–656
- Allon M, Dunlay R, Copkney C. Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; 110(6): 426–429
- Tzamaloukas AH, Avasthi PS. Temporal profile of serum potassium concentration in nondiabetic and diabetic outpatients on chronic dialysis. *Am J Nephrol* 1987; 7(2): 101–109
- Palevsky PM. Hyponatremia. *Semin Nephrol* 1998; 18(1): 20–30
- Bia MJ, DeFronzo RA. Extrarenal potassium homeostasis. *Am J Physiol* 1981; 240(4): F257–F268
- Brennan BL, Yasumura S, Letteri JM et al. Total body electrolyte composition and distribution of body water in uremia. *Kidney Int* 1980; 17(3): 364–371
- Ahmed J, Weisberg LS. Hyperkalemia in dialysis patients. *Semin Dial* 2001; 14(5): 348–356
- Allon M. Hyperkalemia in end-stage renal disease: mechanisms and management. *J Am Soc Nephrol* 1995; 6(4): 1134–1142
- Gruy-Kapral C, Emmett M, Santa Ana CA et al. Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol* 1998; 9(10): 1924–1930
- Blumberg A, Weidmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int* 1992; 41(2): 369–374
- Gutierrez R, Schlessinger F, Oster JR et al. Effect of hypertonic versus isotonic sodium bicarbonate on plasma potassium concentration in patients with end-stage renal disease. *Miner Electrolyte Metab* 1991; 17(5): 297–302
- Liou HH, Chiang SS, Wu SC et al. Hypokalemic effects of intravenous infusion or nebulization of salbutamol in patients with chronic renal failure: comparative study. *Am J Kidney Dis* 1994; 23(2): 266–271
- Liou HH, Chiang SS, Wu SC et al. Intravenous infusion or nebulization of salbutamol for treatment of hyperkalemia in patients with chronic renal failure. *Zhonghua Yi Xue Za Zhi (Taipei)* 1994; 53(5): 276–281
- Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int* 1990; 38(5): 869–872
- Ho K. A critically swift response: insulin-stimulated potassium and glucose transport in skeletal muscle. *Clin J Am Soc Nephrol* 2011; 6(7): 1513–1516
- DeFronzo RA, Felig P, Ferrannini E et al. Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. *Am J Physiol* 1980; 238(5): E421–E427
- Emmett M. Non-dialytic treatment of acute hyperkalemia in the dialysis patient. *Semin Dial* 2000; 13(5): 279–280
- Kim HJ, Han SW. Therapeutic approach to hyperkalemia. *Nephron* 2002; 92 Suppl 1: 33–40
- Williams PS, Davenport A, Bone JM. Hypoglycaemia following treatment of hyperkalaemia with insulin and dextrose. *Postgrad Med J* 1988; 64(747): 30–32
- Schafers S, Naunheim R, Vijayan A et al. Incidence of hypoglycemia following insulin-based acute stabilization of hyperkalemia treatment. *J Hosp Med* 2012; 7(3): 239–242
- Blumberg A, Weidmann P, Shaw S et al. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med* 1988; 85(4): 507–512
- Sequist ER, Anderson J, Childs B et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; 36(5): 1384–1395
- Defining and Reporting Hypoglycemia in Diabetes: A report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; 28(5): 1245–1249
- Brutsaert E, Carey M, Zonszein J. The clinical impact of inpatient hypoglycemia. *J Diabetes Complications* 2014
- Stahn A, Pistrosch F, Ganz X et al. Relationship Between Hypoglycemic Episodes and Ventricular Arrhythmias in Patients With Type 2 Diabetes and Cardiovascular Diseases: Silent Hypoglycemia and Silent Arrhythmias. *Diabetes Care* 2014; 37(2): 516–520
- Apel J, Reutrakul S, Baldwin D. Hypoglycemia in the treatment of hyperkalemia with insulin in patients with end-stage renal disease. *Clin Kidney J* 2014; 7(3): 248–250
- Haviv YS, Sharkia M, Safadi R. Hypoglycemia in patients with renal failure. *Ren Fail* 2000; 22(2): 219–223
- Ginsberg JS, Zhan M, Diamantidis CJ et al. Patient-Reported and Actionable Safety Events in CKD. *J Am Soc Nephrol* 2014
- Stumvoll M, Chintalapudi U, Perriello G et al. Uptake and release of glucose by the human kidney. Postabsorptive rates and responses to epinephrine. *J Clin Invest* 1995; 96(5): 2528–2533
- Mitrakou A. Kidney: its impact on glucose homeostasis and hormonal regulation. *Diabetes Res Clin Pract* 2011; 93 Suppl 1: S66–S72
- Leyking S, Fliser D. Insulin Resistance in CKD. *Clinical Journal of the American Society of Nephrology* 2014; 9(4): 638–640
- Williams ME, Garg R. Glycemic management in ESRD and earlier stages of CKD. *Am J Kidney Dis* 2014; 63(2 Suppl 2): S22–S38
- Abe M, Kaizu K, Matsumoto K. Plasma insulin is removed by hemodialysis: evaluation of the relation between plasma insulin and glucose by using a dialysate with or without glucose. *Ther Apher Dial* 2007; 11(4): 280–287
- Burmeister JE, Scapini A, da Rosa Miltersteiner D et al. Glucose-added dialysis fluid prevents asymptomatic hypoglycaemia in regular haemodialysis. *Nephrol Dial Transplant* 2007; 22(4): 1184–1189
- Ahee P, Crowe AV. The management of hyperkalaemia in the emergency department. *J Accid Emerg Med* 2000; 17(3): 188–191
- Chothia MY, Halperin ML, Rensburg MA et al. Bolus Administration of Intravenous Glucose in the Treatment of Hyperkalemia: A Randomized Controlled Trial. *Nephron Physiol* 2014; 126(1): 1–8
- Ljutic D, Rumboldt Z. Should glucose be administered before, with, or after insulin, in the management of hyperkalemia? *Ren Fail* 1993; 15(1): 73–76
- Ngugi NN, McLigeyo SO, Kayima JK. Treatment of hyperkalaemia by altering the transcellular gradient in patients with renal failure: effect of various therapeutic approaches. *East Afr Med J* 1997; 74(8): 503–509

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