Abnormalities of serum potassium concentration in dialysis-associated hyperglycemia and their correction with insulin: a unique clinical/physiologic exercise in internal potassium balance

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Abstract The absence of significant losses of potassium in the urine makes dialysis-associated hyperglycemia (DH) a model for the study of the internal potassium balance. Studies of DH have revealed that hyperkalemia is frequent at presentation, insulin infusion is usually the only treatment required, and the magnitude of the decrease in serum potassium concentration (K⁺) during treatment of DH with insulin depends on the starting serum K⁺ level, the decreases in serum glucose concentration and tonicity, and the increase in serum total carbon dioxide level. We present an analysis of these findings based on previously studied actions of insulin. Calculations of transcellular potassium shifts based on the combined effects of insulin—the increase in the electrical potential differences (hyperpolarization) of the cell membranes and the correction of the hyperglycemic intracellular dehydration through decrease in serum glucose concentration—produced quantitative predictions of the decrease in serum K⁺ similar to the reported changes in serum K⁺ during treatment of DH with insulin. The lessons from analyzing serum K⁺ changes during treatment of DH with insulin are applicable to other conditions where internal potassium balance is called upon to protect serum K⁺, such as the postprandial state. The main questions related to internal potassium balance in DH that await clarification include the structure and function of cell membrane potassium channels,

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the effect of insulin on these channels, and the mechanisms of feedforward potassium regulation.

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**Introduction**

The large urinary losses of water and electrolytes that develop in patients with preserved renal function during hyperglycemic episodes, including diabetic ketoacidosis (DKA) and nonketotic hyperglycemia (NKH), are not encountered in dialysis-associated hyperglycemia (DH). The clinical manifestations of DH reflect this absence of external fluid and solute losses [1, 2]. The presenting serum potassium concentration (K\(^+\)) in hyperglycemia reflects a shift of potassium from the intracellular into the extracellular compartment [3]. In the absence of external losses, as is often the case with DH, this shift represents the only hyperglycemic influence on serum K\(^+\). Consequently, the changes in serum K\(^+\) observed during development of DH or its treatment with insulin represent exclusively transcellular shifts of potassium [4].

Transfer of potassium between the two major fluid compartments constitutes the internal potassium balance [5–8], which is critical for the life of multicellular organisms. DH allows, during its development or treatment with insulin and no dialysis, the study of a disturbance of internal potassium balance without any changes in the external balance of potassium or fluid. Insights gained from studying DH and its treatment can be applied to other conditions affecting the internal potassium balance, for example the postprandial state. This review presents an interpretation, based upon the actions of relevant regulators of internal potassium balance, of the cardinal findings in our review of published studies on serum K\(^+\) in DH and its treatment [9].

**The effects of insulin on serum potassium concentration in DH**

This section analyzes the mechanisms underlying two critical findings: (a) dialysis-associated hyperglycemia (DH) is associated with a risk of hyperkalemia and (b) the presenting serum K\(^+\) and the decrease in serum glucose concentration and tonicity during treatment of DH with insulin account for the greatest part of the change in serum K\(^+\) during treatment of DH [9]. That insulin absence is the most important factor in the development of hyperkalemia in hyperglycemic syndromes has been recognized [10, 11]. Insulin absence and insulin administration have several actions on internal potassium balance and consequently on serum K\(^+\). We will discuss here the effects of insulin on the internal potassium balance in DH. These effects are direct, through an effect on the function of the cell membrane, and indirect. The indirect insulin effects are mediated through correction of hyperglycemic abnormalities, such as hypertonicity and metabolic acidosis, and are potentially multiple.

**Direct effect of insulin on internal potassium balance**

A direct effect of insulin deficit on internal potassium balance was demonstrated by infusions of somatostatin, which inhibits insulin secretion at least partially, into different groups of subjects. After somatostatin infusion, serum K\(^+\) did not change in patients with type 1 diabetes and increased by 0.5–0.6 mmol/L in patients with type 2 diabetes, normal subjects, and normal dogs, while serum glucose concentration did not show any changes. The somatostatin-induced rise in serum K\(^+\) was prevented in normal dogs by simultaneous infusion of insulin [12].

The direct effect of insulin on internal potassium balance is independent of the presence or absence of glucose in the extracellular compartment [13–16] and is the result of an increase in the activity of the Na\(^+\), K\(^+\)-ATPase of the cell membranes [17–19]. Immunoelectron microscopy studies detected a robust (between 1.5 and 3.7-fold) insulin-mediated increase in the numbers of immunolabeled alpha-2 subunits of this enzyme in the membrane of mammalian muscles [20].

The Nerst equation (see Appendix) expresses the transmembrane electrical potential gradient (\(E_K\)) as a function of the ratio of potassium concentrations in the extracellular and intracellular fluid ([K\(^+\)]\(_e\)/[K\(^+\)]\(_i\)). This arrangement suggests that the ratio [K\(^+\)]\(_e\)/[K\(^+\)]\(_i\) determines the value of \(E_K\). In the steady state (the resting state in excitable tissues), the Nerst relationship holds true at a reasonable approximation, with severe illness
a notable exception [21]. The relationship between insulin and internal potassium balance was evaluated by analyzing changes in $E_K$ and in the ratio ($[K^+]_i/[K^+]_e$) caused by the actions of insulin.

Zierler studied the changes in intracellular potassium content and $E_K$ after addition of insulin to baths containing excised rat extensor digitorum longus muscles in solutions with appropriate composition. After addition of insulin to the bath, $E_K$ increased by a mean of 5.4 mV within about 30 min, while the increase in intracellular potassium content, by 10%, required 2–3 h [13]. This study illustrated an important fact about internal potassium balance: Unlike the interpretation of the Nernst equation previously presented, it is changes in the $E_K$ that determine, to a certain extent, cellular uptake or loss of potassium. This fact has both physiological and pathophysiological applications.

Zierler’s study also raised the following critical question: how is it possible, if the ratio $[K^+]_i/[K^+]_e$ is the only determinant of the transmembrane electrical potential difference, as determined by the Nernst equation, to note changes in this electrical potential difference prior to any changes in the $[K^+]_i/[K^+]_e$ ratio? The answer to this question is that the Nernst equation represents an idealized cell membrane containing only potassium-selective channels. In reality, cell membranes contain channels for various ions. The Goldman–Hodgkin–Katz equation (Appendix), which expresses the transmembrane electrical potential gradient ($E_M$) as a function of the intracellular and extracellular concentrations of potassium, sodium, and chloride and of the permeabilities of the cell membrane to these ions, provides a more precise formula for the transmembrane electrical potential difference.

In the steady state, $E_K$ is normally very close to $E_M$ because by far, the highest permeability of cell membranes at rest is the permeability to potassium ions [22]. Insulin and other factors influencing internal potassium balance change various ionic permeabilities of the cell membranes [23]. The main regulator of the voltage across the cell membrane is the probability of open potassium channels in the membrane. Cell membranes have several types of potassium channels that are regulated by voltage, ligands such as calcium ions or metabolites, such as ADP (adenosine diphosphate—the $K_{ATP}^+$ channels). Decreases in intracellular ADP concentration provide the signal for opening of $K_{ATP}^+$ channels, which in addition to regulating transmembrane voltage have a major role in hyperglycemia-stimulated release of insulin [24]. The stereochemical structure and function of potassium channels [25, 26] and the effects of voltage on these two properties of the potassium channels [27] are being investigated. Future developments will clarify the mechanism of insulin action on these channels.

The main indirect effect of insulin on internal potassium balance in DH

The main indirect effect of insulin on internal potassium balance during treatment of dialysis-associated hyperglycemia (DH) is mediated through changes in tonicity. DH is a state of hypertonicity corrected as hyperglycemia is rectified by insulin [2, 9]. Hypertonicity leads to potassium exit from the cells and resultant hyperkalemia [28, 29]. The proposed mechanisms for the development of hyperkalemia in hypertonicity include intracellular dehydration, altered cell membrane function, or altered intracellular metabolism [29]. The last two mechanisms will need to be studied. We will discuss further intracellular dehydration, which allows quantitative predictions of the exit of potassium from the cells in hypertonicity, if it is the only hypertonic abnormality affecting internal potassium balance and if its magnitude is known.

According to the Nernst equation, the ratio $[K^+]_i/[K^+]_e$ must remain the same, if $[K^+]_e$ changes and $E_K$ remains the same. In this instance, $[K^+]_i$ must change in proportion to $[K^+]_e$, so that the fractional (percent) changes in $[K^+]_i$ and $[K^+]_e$ are equal. Consequently, a condition that is necessary, but not sufficient, for concluding that hypertonicity causes hyperkalemia exclusively through intracellular dehydration is that the resting transmembrane electrical potential difference will not change in hypertonic states. Indirect experimental findings suggesting no change in the ratio $[K^+]_i/[K^+]_e$ during development of hypertonicity [29] support the hypothesis that intracellular dehydration is the only or the dominant cause of hypertonicity-related hyperkalemia. In this case, the magnitude (fractional or percent change) of the rise in $[K^+]_i$ caused by hypertonicity is predictable from the Nernst equation when the fractional intracellular dehydration is known.

Measurement of the changes in serum glucose and sodium concentrations during correction of DH allows computation of the fractional changes in extracellular volume and intracellular volume from
the simultaneous changes in serum glucose and sodium concentrations [2, 31, 32]. These computations were applied in the quantitative analysis of the effects of insulin on the fractional changes in intracellular and extracellular volumes in DH that is presented below and in the Appendix.

Integration of the direct and the major indirect insulin effects on serum $K^+$ in DH

The effects of insulin on internal potassium balance through increase in the cell membrane electrical potential difference and correction of hyperglycemic hypertonicity were combined to provide quantitative estimates of the changes in serum $K^+$ after insulin administration in DH. We made the following assumptions: (a) The Nernst equation describes the $[K^+]_e/[K^+]_i$ ratio in the steady state both during hyperglycemia and after its correction with insulin. (b) The only determinants of the change in serum $K^+$ during insulin treatment of DH are the direct effect of insulin on the cell membrane and the correction of the intracellular dehydration as serum glucose concentration decreases. And (c) the extracellular-to-intracellular volume ratio ($V_e/V_i$) is 1:2 during euglycemia, increases during hyperglycemia as a result of the osmotic fluid shift from the intracellular into the extracellular space, and returns to the 1:2 value as hyperglycemia is corrected by insulin.

We calculated the changes in $[K^+]_e$ during development of DH in patients with hypothetical anuria presenting with the same degree of hyperglycemia (66.6 mmol/L) and varying initial $[K^+]_e$. The increase in serum glucose concentration—and therefore in tonicity—was the same in all instances. We studied three different scenarios during development of DH: (a) The only change (increase) was in the volume ratio $V_e/V_i$ as hypertonicity developed during development of DH, while the $E_K$ remained constant. Note that the increase in $V_e/V_i$ depends on the increase in serum glucose concentration [1, 4]. (b) The only change (absolute decrease) was in the transmembrane electrical potential difference ($E_K$), while the ratio $V_e/V_i$ remained constant. And (c) changes in $V_e/V_i$ and $E_K$ occurred simultaneously. The Appendix shows the calculations.

In either an isolated change in $E_K$ or an isolated change in the ratio $V_e/V_i$, the higher the presenting serum $K^+$ is, the greater the decline in this concentration during insulin treatment of DH will be. Figure 1 shows the relationship between $[K^+]_e$ and glucose concentrations in a patient with hypothetical anuric hyperglycemia treated with insulin. Data were calculated using the theoretical effects of insulin on the shift of extracellular fluid into the intracellular compartment and on the resting membrane electrical potential difference (see text for details).

Other indirect effects of insulin in DH: other factors affecting internal potassium balance

Beta-adrenergic stimulation from either hyperkalemia accompanying the dialysis-associated hyperglycemia

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Fig. 1 Relationship between extracellular potassium and glucose concentration in a patient with hypothetical anuric hyperglycemia treated with insulin. Data were calculated using the theoretical effects of insulin on the shift of extracellular fluid into the intracellular compartment and on the resting membrane electrical potential difference (see text for details)
(DH) [33] or hypoglycemia developing during treatment with insulin [34] may further decrease serum K\(^+\). Inhibition of hepatic gluconeogenesis by insulin can produce hypokalemia via decreased hepatic glucose release [35]. Correction of ketoacidosis (DKA) may also have a hypokalemic effect [9]. Finally, whether the cellular uptake and intracellular metabolism of glucose have any effect on its own on internal potassium balance has not been studied.

Other factors affecting the internal potassium balance, but extrinsic to insulin, can also affect the presenting serum K\(^+\) in DH and its changes during treatment with insulin. The effects of a catabolic state can be profound. Hyperkalemia- or hypokalemia-inducing drugs, exercise, and body composition can also affect the presenting serum K\(^+\). Uremia affects internal potassium balance by decreasing the activity of the Na\(^+\), K\(^+\)-ATPase [36, 37]. A consequence of this defect is that patients with severe renal failure often have total body potassium deficits in the presence of normal or even high serum K\(^+\) [38]. The uremic defect in the Na\(^+\), K\(^+\)-ATPase is acutely corrected by hemodialysis [39]. These observations raise the questions of the effects of the correction of uremia (adequacy of dialysis) and of the temporal relationship between DH and hemodialysis sessions on the presenting serum K\(^+\) in DH and its change during treatment.

Factors affecting the external potassium balance in DH

Changes in the external balance of potassium may have major effects on both the presenting serum K\(^+\) in DH and its changes during treatment with insulin. These changes are mediated through dietary potassium intake and external losses through the gastrointestinal tract, the urine in patients with significant residual renal function, and rarely the skin, and through dialysis. The modality of dialysis is a factor affecting serum K\(^+\) in DH that requires further discussion.

Potassium removal by hemodialysis (HD) sessions can vary substantially depending on the serum K\(^+\) at the start of the session, the dialysate potassium concentration, the blood and dialysate flows, the type of dialyzer used, and the duration of the session, but is usually large. The maximal amount of potassium that can be removed daily by peritoneal dialysis (PD) is the product of the daily drain volume and serum potassium concentration and is usually 30–50 mmol. Higher serum K\(^+\) levels have been reported in nonketotic hyperglycemia (NKH), but not in DKA, in patients on HD than in those on PD [9]. Hypokalemia, which is relatively frequent in PD patients without hyperglycemia, cannot be explained by changes in the external balance of potassium [40], but was attributed to changes in the internal potassium balance through increased insulin secretion rate stimulated by the glucose absorbed from the dialysate or other digestive stimuli [40, 41]. In PD patients with DH, high secretion rates of aldosterone and relatively high serum levels of total carbon dioxide may also contribute to the relatively low serum K\(^+\) [42].

The calculations made in the previous sections did not include potassium removal by dialysis, because the intent of these calculations was to compute the effects of DH and insulin on the internal potassium balance and to compare these calculations to findings of studies of the effects of insulin administration on serum K\(^+\) [9], in which dialysis was not performed during treatment of DH.

Summary of insulin actions: applications to other examples of internal potassium balance

The regulation of serum K\(^+\) during treatment of DH with only one agent, insulin, is complex. The major hypokalemic effects of the infused insulin are mediated through the change (absolute increase) in \(E_K\), the correction of intracellular dehydration through fluid shift from the extracellular compartment, which is a direct consequence of the decrease in serum glucose concentration, and the presenting serum K\(^+\). Correction of DKA or hypertonic dilution acidosis [43] may have minor hypokalemic effects. The effects of factors not related to DH or insulin can be variable. Finally, it is not clear whether correction of hypertonicity outside the attendant change in extracellular and intracellular volumes or the transfer and metabolism of glucose intracellularly has independent effects on internal potassium balance.

Understanding of the multiple insulin actions in DH facilitates the detection of factors operating on internal potassium balance independently of insulin during treatment of DH. For example, a rising or even unchanging serum K\(^+\) during treatment of DH should
Recent developments in our understanding of internal potassium balance

The regulation of the external and internal balances of potassium is the subject of ongoing studies [44]. A development that has a bearing on the topic of the present review is that of the feedforward control of potassium balance. The classical feedback concept of regulation of serum K\(^+\) states that appropriate regulatory factors directed toward both the external and internal balance are activated by changes in serum K\(^+\). In contrast, the feedforward concept refers to the rapid detection, not of changes in K\(^+\) but of potassium movement into the extracellular compartment through sensors strategically placed in tissues such as the wall of the gut and the vascular bed of skeletal muscles. These sensors detect the movement of potassium during potassium absorption from the gut after a meal or egress from the muscles during exercise, and activate effector mechanisms prior to the development of hyperkalemia [45–47].

The feedforward control of external potassium balance has been studied in greater detail than that of the internal potassium balance. Nevertheless, there is some information available on feedforward control of internal potassium balance in exercise and in muscle ischemia. These conditions lead to potassium efflux from the muscles and an increase in intracellular adenosine monophosphate (AMP) concentration, which activates a protein kinase (AMP-activated protein kinase) responsible for increasing glucose uptake by the muscles [48]. Activation of the same enzyme leads to cellular potassium uptake [49]. Whether this or other mechanisms of feedforward control of internal potassium balance are operative in DH and other conditions leading to hyperkalemia would be an interesting topic for study in the future.

Conclusions

The value of DH as an exercise in Physiology is that it provides a model for the study of internal potassium balance in a clinical setting, which can duplicate experimental requirements (only one intervention, insulin infusion). Important but currently unavailable information about this entity is the electrical potential gradient across muscle cell membranes at the time of presentation with DH, its changes after insulin administration, and the relationship of these changes to the transcellular movements of potassium. Obtaining this information may be feasible, because methods for measuring the electrical potential difference across muscle cell membranes in clinical settings have been reported [21, 38, 50]. Other questions that can be answered through study of DH include whether intracellular dehydration is the only cause of hyperkalemia in hypertonic states and whether diabetic ketoacidosis represents a separate hyperkalemic risk. Lessons learned from the study of DH are applicable in understanding of the mechanisms of other conditions in which the internal balance is called upon to defend serum potassium concentration.

An Appendix with the following list of topics is available online:

Abbreviations and Definitions

Computation of insulin effects on internal potassium balance

(A) Development of dialysis-associated hyperglycemia. Total body potassium constant

1. Effects of hypertonicity on the extracellular and intracellular volumes
2. Effects of insulin absence through depolarization of the cell membrane

(B) Food intake: Changes in total potassium

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