Vol 8|Issue 1| 2018 |1-11.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

HYPERKALAEMIA TOPIC REVISITED

Alosaimi, Abdullah[1,2]

[1]School of Pharmacy and Medical sciences, University of South Australia.
[2]King Faisal Specialist Hospital and Research Centre, Saudi Arabia.

ABSTRACT

Hyperkalaemia is a medical emergency requiring timely intervention. Where clinically indicated, corrective measures must be initiated to manage hyperkalaemia, as well as any underlying disorder that might have contributed to the condition or that will interfere with its correction. Data analysis suggests that elderly patients are especially vulnerable because they are prone to various risk factors such as reduced renal function, diabetes mellitus, and the use of various medications that interfere with potassium homeostasis. When treatment involves medications associated with hyperkalaemia, patient monitoring is essential. Conventional approaches to management were effective in the management of the majority of cases in this study.The goal of this extensive review article was to review all English literatures available to understand the potassium homeostasis and hyperkalaemia aetiology, risk factors, adverse effects, diagnosis, and clinical management and response to treatment.

Key words: Conventional approaches, Potassium homeostasis, Various medications.

INTRODUCTION

Hyperkalaemia is thought to occur in about 1–9% of inpatients [1]. Often, this is attributed to hyperglycemia, renal failure, or incorrect usage of potassium supplements. Hyperkalaemia is a common cause of morbidity. Significant hyperkalaemia interferes with cardiac function [2]. The rate of mortality may be as high as 67% if severe hyperkalaemia is not treated quickly [3].

The human body's capacity to adjust efficiently to large loads of potassium usually prevents increases of serum potassium from exceeding the normal reference range's upper limit. Therefore, to develop hyperkalaemia it is usually necessary for a defect to exist in one or more mechanisms that sustain potassium homeostasis. Factors that can affect these mechanisms are classifiable into three categories: a rise in potassium load; a decline in excretion of kidney potassium; and shifts in transcellular potassium.

Potassium (K^+) is the principal cation in intracellular fluid. The overall potassium load in the body is estimated to be 50 mmol/kg, with 98% of this found intracellularly. In most situations, the values of serum and plasma potassium fall in the range of 10% of one another and could be considered indistinguishable. The distribution of all body potassium across the extracellular and intracellular spaces leads to a large gradient of potassium concentration across these two compartments. The approximate concentration of intracellular potassium is 150 mmol/L whereas the extracellular concentration stands at an estimated 4 mmol/L. Since the membrane resting Latency depends on the intracellular/extracellular ratio of potassium concentration, minute shifts within the smaller extracellular concentration could lead to considerable variations in the electrical cell properties. Therefore, sustaining this potassium gradient is critical and depends on various processes. These include potassium distribution across the extracellular and intracellular compartments, potassium's renal secretion, and dietary potassium load [3].

Literature Review

Maintaining normal potassium homeostasis

Estimates on the daily intake of potassium in a regular diet are between 50 and 90mmol. Of this, about 90% is excreted renally. This excretion appears to be slow. Around 50% of a potassium load is eliminable in a four to six hour period [1].

Factors that affect excretion of renal potassium include delivery of distal sodium, the influences of vasopressin and the renin-angiotensin-aldosterone system, rate of urine flow, serum potassium concentration, acid-base status, and dietary potassium intake. Basal catecholamines and insulin concentration, acid-base status, parathyroid hormone, and thyroid hormone influence

*Corresponding Author **Abdullah** E mail: aosaimi@gmail.com

extrarenal potassium handling [4].

Renal maintenance of potassium homeostasis

The kidneys are the major organ for maintaining potassium homeostasis, excreting more than 90% of the daily potassium load. The kidneys are also responsible for long-term potassium homeostasis. Secretion of potassium into the distal nephron's lumen is passive. This passive potassium movement depends on the gradient of concentration between the lumen negative electrical gradient (which is fundamentally produced by reabsorption of sodium) favouring secretion, the luminal membrane, and the luminal membrane permeability towards potassium.

In potassium regulation through renal mechanisms, aldosterone plays a major role, increasing the secretion of potassium by acting on cells within the connecting tubules, the collecting duct, and the principal medullary and cortical collecting tubule cells. At a cellular level, aldosterone facilitates Na^+-K^+ ATPase action and opens apical sodium channels at the baso-lateral membranes. This results in an increased secretion of potassium. Aldosterone arbitrates its influence upon binding to receptors within the cell nucleus. Additionally, aldosterone influences extrarenal control of potassium secretion through elevations in salivary and colonic potassium secretion [5]. Usually, the gut accounts for only 5% of the entire potassium excretion. However, this can rise significantly to be responsible for 30% to 50% of potassium excretion in persons diagnosed with kidney disease [6]. In the potassium movement to the transcellular compartment, aldosterone may play a role as well.

The concentration of serum potassium directly affects the excretion of potassium into the urine, an effect that does not depend on its capacity to raise the concentrations of aldosterone.

On the other hand, urine flow and distal sodium delivery influence urinary potassium excretion. A rise in potassium secretion also occurs in settings where there is increased urine flow and distal sodium delivery. Conditions that reduce the delivery of sodium in the distal tubule diminish the excretion of urinary potassium, in a manner similar to reductions in urine flow associated with either decreased kidney function or volume depletion.

External maintenance of potassium homeostasis

The influence of insulin in maintaining potassium homeostasis is subject to mediation through the direct uptake of potassium intracellular stimulation by Na^+-K^+ ATPase at fat cells, skeletal muscle, and the liver. In diabetic cases characterized with insulin deficiency, a reduction in hepatic potassium uptake and muscle tissue occurs. Insulin's potassium lowering effect is not dependent on adrenergic stimulation. However, the hypokalemic effects of insulin are dependent on dose.

Selective Beta2-adrenergic agonists promote potassium's intracellular uptake through Na^+-K^+ ATPase stimulation in regular human subjects. Epinephrine and salbutamol (albuterol) administration lowers the concentration of potassium. This effect is blocked by non-selective beta-blockers. Adrenergic agonists such as phenylephrine elevate serum potassium through the impairment of potassium's intracellular uptake, an effect that the alpha-adrenergic antagonist phentolamine's concomitant administration blocks.

Phenylephrine has no effect on the excretion of urinary potassium or concentrations of insulin, aldosterone, or renin. In standard situations, the elevation in production of catecholamines associated with vigorous exercise and eating diminishes the elevations in the concentration of serum potassium, which would otherwise be an outcome of potassium secretion from muscle cells or absorption from the gut [7]. On the other hand, Beta2-adrenergic agonists can be effective as a therapeutic option for hyperkalaemia treatment.

Concerning the status of acid-base, there is a general belief that a 0.7mmol/L rise in concentration of potassium occurs for every 0.1 reduction in the pH in acute acidosis cases [8]. Conversely, there have been indications of an inverse association in cases of acute metabolic alkalosis characterised by a rise in the uptake of potassium intracellularly in exchange for ions of hydrogen leading to a reduction in the serum concentration of potassium. Closer assessment of the studies that initially reported these changes, as well as subsequent studies, reveals substantive inconsistency in the serum potassium rise—ranging between 0.4mmol/Land 1.4mmol/L per one unit reduction in pH. Additionally, the relationship between concentration of potassium and pH is not exhibited reliably in all acidosis etiologies. The relationship between chronic acid-base disorders and serum potassium dynamics exhibit considerable variability and is oftentimes unpredictable.

Potassium adaptation

The potassium adaptation process startsafter eating a meal with high potassium and increases with additional intake of potassium. This adaptation happens largely because of an elevation in excretion of potassium in urine, along with the intracellular rate of potassium uptake being faster. A rise in colonic potassium secretion also occurs. The rise in secretion of aldosterone linked with elevations in the concentration of serum potassium facilitates the potassium adaptation process [9]. Although some potassium adaptation happens following adrenalectomy, a complete response is dependent on aldosterone.

Potassium adaptation constitutes a critical mechanism for the maintenance of normokalemia in people with impaired kidney function, provided there is no excessive potassium intake. These individuals have an increased count and activity of the Na+/K+-ATPase channels in their remaining functional kidneys, leading to increased fractional secretion of potassium. Furthermore, there is a considerable rise in colonic potassium secretion, coupled with increased Na+/K+-ATPase activity within the colonic mucosa. Hyperkalaemia could occur in the context of various degrees of kidney function impairment in those diagnosed with kidney disease [10, 11]. At any extent of kidney function, hyperkalaemia is more likely to

occur alongside concurrent medical conditions such as insulin insufficiency, or during use of angiotensin converting enzyme (ACE) inhibitors.

Definition of hyperkalaemia

Normal concentrations of serum potassium range between 3.5 and 5 mmol/L, whereas the definition of hyperkalaemia is a concentration of potassium in plasma in excess of 5.5 mmol/L [12, 13].

Epidemiology

Hyperkalaemia is thought to occur in about 1–9% of inpatients. Often, this is attributed to hyperglycemia, renal failure, or incorrect usage of potassium supplements. Hyperkalaemia is a common cause of morbidity. Significant hyperkalaemia interferes with cardiac function. The rate of mortality may be as high as 67% if severe hyperkalaemia is not treated quickly [14-16].

Causes of hyperkalaemia

The human body's capacity to adjust efficiently to large loads of potassium usually prevents increases of serum potassium from exceeding the normal reference range's upper limit. Therefore, to develop hyperkalaemia it is usually necessary for a defect to exist in one or more mechanisms that sustain potassium homeostasis. Factors that can affect these mechanisms are classifiable into three categories: a rise in potassium load; a decline in excretion of kidney potassium; and shifts in transcellular potassium.

Increase in potassium load

Both exogenous and endogenous sources can lead to increased potassium concentrations in the extracellular compartment. Foods especially rich in potassium (in excess of 6.4 mmol per serving) include citrus juices and fruits, bananas, tomatoes, tomato juice, honeydew melons, potatoes, cantaloupes, peaches, and salt substitute. Oftentimes, people tend to overlook herbal medicines as an exogenous potassium source. An example is *Morinda citrifolia* (noni juice, which contains 14 mmol in a standard 8 fluid ounce serving) [17-19].

Therapeutic products and medications can also present considerable loads of potassium. Examples include protein-calorie supplements, potassium chloride itself, penicillin products, stored blood, and Collins solution. In general, the concentration of potassium in the serum of stored blood rises by 1 mmol/L per day. This rise depends on how much time the blood is stored as well as the type of preservative used. The preservative in Collin's solution contains 141 mmol/L of potassium and its usage has led to hyperkalaemia following cadaveric kidney transplantation [20].

Generally, the human body adeptly handles potassium acquired from exogenous sources over time. However, if the homeostatic mechanism is impaired through lack of insulin, impaired renal function, or following the rapid administration of huge quantities of potassium, it is possible to overwhelm these systems. For instance, a single 0.5 mmol/kg dose of potassium chloride does not greatly increase the concentration of serum potassium. However, if the renal function is impaired, a dosage as small as 35 to 45 mmol could trigger hyper kalaemia [21].

Endogenous secretion of potassium happens in the presence of increased cellular tissue breakdown. In addition, potassium secretion occurs from skeletal muscles under the mediation of adenosine triphosphate (ATP) and the subsequent opening of potassium channels of the adenosine triphosphate-dependent skeletal muscles during exercise. Usually, this transitory alteration in the concentration of serum potassium is asymptomatic, and the concentration returns to pre-exercise levels about five minutes after exercise cessation. An increase in serum potassium concentration could occur at lower exercise levels in patients with coronary artery disease.

Acute tumor lysis syndrome and Rhabdomyolysis could lead to hyperkalaemia attributed to potassium secretion. Acute tumor lysis develops in people upon treatment of certain types of cancers, but can occur spontaneously with tumours with rapid cell growth and turnover. Often, acute tumor lysis syndrome appears in individuals with acute leukemia or Burkett's lymphoma, although it is not exclusive to these disorders. Hyperkalaemia developing in acute tumor lysis syndrome is multifactorial and develops because of transcellular shift associated with acute metabolic acidosis, rapid lysis of a large cell burden, and reduced renal excretion in the case of renal failure development from hyperuricemia. Acute hyperkalaemiais also associated with acute rhabdomyolysis [22]. The potassium efflux from the extracellular into the intracellular compartment, which is either related to trauma or can be drug-induced, and exacerbated by the development of acute myoglobinuric renal failure, could lead to sustained hyperkalaemia.

Interruption of the secretion of distal tubule potassium can be linked with decreased kidney functioning mediated by any cause. An elevated risk of hyperkalaemia is thus attributable to factors that directly impair the distal tubule structure as well as those that have an effect on its function. Structural kidney changes associated with hyperkalaemia that lead to morbidity disproportionate to the extent of kidney dysfunction include systemic lupus erythematosus, kidney transplantation, amyloidosis, obstructive uropathy, and sickle cell disease [23-25]. Moreover, any condition leading to tubular atrophy or tubulointerstitial fibrosis will most likely trigger damages in the secretion of renal tubular potassium. These derangements could appear despite relative preservation of the GFR (glomerular filtration rate) [26].

HRHA (hyporeninemic hypoaldosteronism) is a disorder that involves decreased concentrations of aldosterone and renin. Usually, hypoaldosteronism is multifactorial [27], and can be associated with fatal hyperkalaemia.

Decrease in kidney excretion of potassium

Chronic depletion of extracellular volume associated with the use of frusemide is capable of partially restoring aldosterone secretion, thus implying that renin insufficiency is causative. However, hyperkalaemia ought

to promote the secretion of aldosterone without depending on renin secretion, and fludrocortisone doses exceeding the standard replacement dose are necessary to correct potassium excretory defect. Therefore, this defect could be either post-receptor or intra-adrenal.

HRHA can be induced by several pharmacological agents. In addition, hyperkalaemia is an aldosterone deficiency feature that results from adrenal deficiency. Causes include haemorrhage, autoimmune destruction, and adrenal infections including HIV-related cytomegalovirus.

Hyperkalaemia can exist in situations that lower delivery of distal sodium and urine flow. These situations are normally associated with oedema such as cirrhosis, nephrotic syndrome, and congestive heart failure. In general, hyperkalaemia arising from cirrhosis and congestive heart failure is mild. However, people suffering from these conditions frequently have coexistent risk factors for hyperkalaemia, such as advanced age or diabetes. Often, their treatment involves agents that could influence potassium excretion like angiotensin receptor blockers(ARBs), spironolactone, or ACE inhibitors [1].

Transcellular shift

Hyperglycemiain poorly controlled diabetes mellitus or after glucose administration without insulin is linked with a rise in concentration of serum potassium. The average rise may range from 0.1 to 2.0 mmol/L [28]. This elevation can occur in the absence of concurrent hypoaldosteronism. Somatostatin-associated hyperkalaemia is most likely a result of suppressed insulin release, which impairs intracellular potassium uptake. It also leads to elevations in extracellular potassium concentration [29].

Administration of amino acids such as ε-aminocaproic acid, arginine, and intravenous lysine results in a shift of potassium to the extracellular from the intracellular space compartment [28]. This transcellular movement does not depend on pH and is proportional with amino acid serum concentration. In people with normal renal function, the administration of intravenous arginine raises serum potassium in the ranges of0.6 mmol/L and 1 mmol/L. A concomitant rise in the excretion of renal potassium counterbalances the rise in concentration of extracellular potassium. Increases in serum potassium that range between 0.6 mmol/L and 1.5 mmol/L have been reported in people with and without kidney failure following amino acid administration [30].

Adrenal insufficiency

The possibility of adrenal deficiency must be considered in every patient diagnosed with hyperkalaemia. The presence of muscular weakness and hyponatremia call for clinical attention. The best screening for primary adrenal deficiency is with a standardised cosyntropin-stimulation test, with the measuring of plasma cortisol level 45 to 60 minutes after. Values below 20 mcg per dL indicate adrenal insufficiency [29].

Congenital causes

Congenital abnormalities can also lead to hyperkalaemia. Some types of congenital disorders result in electrolyte imbalances in neonates, and can be life-threatening if not soon corrected. Should these patients survive infancy, the severity of the disorder tends to decline with age [31].

Drug-induced hyperkalaemia

As discussed earlier, the factors that decrease excretion of potassium also carry the risk of drug-induced hyperkalaemia due to the comparative reduction in renal function with age.

There are common associations of hyperkalaemia with potassium-sparing diuretics (including plerenone, spironolactone, amiloride, and triamterene). Generally, these drugs lead to hyperkalaemiain the initial 10 days of usage coupled with a rate of incidence ranging between 4% and 19%. Fatal hyperkalaemia can result from using these medications by individuals who have extra impairments in potassium homeostasis. In individuals with ESRD (end-stage renal disease), this spironolactone hyperkalemic impact has also been reported. This does not come as a surprise, considering the known effects of aldosterone on potassium's gastrointestinal and cellular handling [28].

There is an association with higher hospital admissions for hyperkalaemia following treatment using trimethoprim-sulfamethoxazole with spironolactone. Avoiding this drug combination is recommended [32]. Trimethoprim, which is an inhibitor of dihydrofolate reductase enzyme, blocks sodium channels and interrupts renal tubular potassium release [33]. Trimethoprim' santikaliuretic influence can be reduced by increasing urine pH and raising the rate of urine flow with medications such as frusemide. In one study the incidence of hyperkalaemia was reported to stand at 21.2% among in patients treated with trimethoprim-sulfamethoxazole. These patients exhibited an average increase in concentrations of serum potassium of 1.21 mmol/L, reaching peak levels after 4.6 days [33].

NSAIDs (nonsteroidal anti-inflammatory drugs) trigger hyporeninemic hypoaldosteronism by impairing production of prostaglandins I2and E2 [34]. In addition to stimulation of renin synthesis, these two prostaglandins stimulate the opening of high-conductance potassium channels that assist in the facilitation of potassium secretion in the distal tubules. Additionally, NSAIDs trigger vasoconstriction, which impairs the delivery of water and salt to the distal tubule. Initially, these agents' hyperkalemic effects were defined with indomethacin in spite of actually being a class impact that occurs with both COX 1/COX 2 non-selective (cyclooxygenase 1/2) inhibitors and COX 2selective inhibitors [35]. Usually, the peak level in potassium concentration occurs within three days to a week of use. Furthermore, NSAIDs can trigger hyperkalaemia by producing acute renal failure.

ACE inhibitors reduce aldosterone secretion mediated by renin and can reduce GFR and further interrupt the secretion of potassium. Individuals with effective/true volume depletion, impaired kidney function,

and renal artery stenosis have increased risk for these agents' adverse effects. There are suggestions that 10% of outpatients, and 9%–36% of inpatients who receive ACE inhibitors will develop hyperkalaemia [36]. With the rise in hyperkalaemia risk inversely proportional to level of kidney function, an elevation in serum potassium could occur within a week after treatment. In one study, at least 7.8% of elderly individuals admitted to hospital for hyperkalaemia were due to secondary usage of ACE inhibitors with diuretics (potassium sparing diuretics) [37].

ARBs lower the effect of angiotensin-II, there by leading to an aldosterone decline. The decrease in concentrations of urinary and serum aldosterone equals that obtained by ACE inhibitors. Hyperkalaemia incidence is also the same, standing at 1.5% (ARBs) and 1.3% (ACE inhibitors) among healthy individuals. There have been observations of increased hyperkalaemia incidence among 7% of elderly people receiving ARBs.

Cyclosporine and tacrolimus trigger hyperkalaemia by reducing Na^+-K^+-ATPase activity, directly inhibiting potassium channels in the collecting tubules. There have been many reports indicating hyperkalaemia incidence via these agents, which may be caused by impaired kidney function. Reports indicate that the incidence among individuals exhibiting no nephrotoxicity to be on the order of 9% [38, 39].

Hyperkalaemia induced by heparin occurs secondary to interference with the synthesis of aldosterone by inhibiting corticosterone transformation in the adrenal glands. Hyperkalaemia is thought to occur in 8% to 17% of patients with heparin [40]. The potassium secretion inhibition occurs after 1–3 days of use and is maximal at 3–5 days. There are also observations of hyperkalaemia with low molecular weight preparations and heparinoids, notwithstanding the dosage or administration route [41, 42].

Digitalis derivatives at toxic concentrations can lead to hyperkalaemia. Among those individuals who develop hyperkalaemia through digitalis poisoning, there is a heightened risk of death should the serum potassium exceed 5.5 mmol/L [43, 44]. In general, though, therapeutic digitalis concentrations do not trigger hyperkalaemia.

Mannitol, like glucose, is osmotically active and has the potential to trigger hyperkalaemia through transcellular shift with solute drag [45].

Beta-adrenergic blockers may cause hyperkalaemia through their direct impedance of cellular uptake of potassium. The blockage of catecholamine-stimulated renin secretion leads to a decline in aldosterone synthesis [46, 47]. Among kidney transplant patients being treated for postoperative hypertension, and persons receiving hemodialysis, the use of labetalol, the receptor antagonist comprising α-, β-adrenergic, was reported to cause hyperkalaemia [48, 49].

Diet and hyperkalaemia

Foods rich in potassium (i.e. having more than 6.4 mmol/serving) can increase serum potassium, especially in patients with renal failure. A patient with hyperkalaemia has to be aware of the amount of potassium in certain foods. These foods include bananas (1 medium banana contains approximately 12 mmol), oranges (5 mmol per small orange), roasted almonds (5 mmol per oz), mushrooms (14 mmol per cup), spinach (22 mmol per cup), grapefruit (12 mmol each), and potatoes (15 mmol each) [50].

There are several ways to reduce the potassium in vegetables. Soak raw vegetables in water for at least two hours, using a 10:1 ratio of water to vegetables. Also, cooking vegetables in plenty of water will pull out some of the potassium [51].

Pseudohyperkalemia

Pseudohyperkalemia refers to serum potassium being artificially elevated *in vitro*. This occurs when laboratory potassium reports fail to reflect actual values(1). Red cells' haemolysis in phlebotomy specimens constitutes the most frequent trigger. Other triggers involve traumatic venipuncture, lab test error, and unusual genetic syndromes such as hereditary spherocytosis and familial pseudohyperkalemia.

Potassium released from platelets could result in falsely high potassium concentrations within a blood sample that is allowed to clot during the collection of serum. Pseudohyperkalemia is exemptible through iterated sample collection as traumatically as possible and acquisition of concentrations of plasma and serum potassium. In spite of increased serum potassium, plasma potassium will be normal among individuals with pseudohyperkalemia [1].

Patients at risk for hyperkalaemia

It is possible for patients with diminished kidney function or diminished delivery of distal sodium and heart failure to take medications that impede the secretion of potassium. Impaired kidney function adds to hyperkalaemia development triggered by rhabdomyolysis, drugs, or other issues.

It is worth noting that elderly people are at more risk for developing hyperkalaemia, because of the many risk factors associated with them. Diabetes mellitus, decreased kidney function, and use of drug-induced hyperkalaemia are the main risk factors in this group [52].

For individuals requiring medications that predispose them to hyperkalaemia, preventive measures are necessary. For example, individuals who use ARBs or ACE inhibitors for renoprotection or cardioprotection may be encouraged to switch to diets with low potassium levels.

In patients with diabetic nephropathy, a sudden serum potassium elevation or changes in electrocardiographic results are an indicator of life-threatening hyperkalaemia. It is imperative to obtain urine osmolarity, potassium and creatinine as an initial stage in the determination of hyperkalaemia's cause, which will guide continuing treatment. Intravenous calcium proves efficacious in undoing electrocardiographic alterations and decreasing arrhythmia risk. However, it does not reduce serum potassium.

Adverse effects of hyperkalaemia

Hyperkalaemia neuromuscular manifestations include flaccid paralysis of the extremities, abdominal pain, diarrhoea, and myalgias [29]. Factors that promote the harmful effects of hyperkalaemia include its development rate in addition to presence of other metabolic derangements such as hypocalcaemia, hyponatremia, or metabolic acidosis.

Diagnosis of hyperkalaemia

Initial diagnosis usually commences with a review of the patient's clinical history, medications, and a physical examination. Signs and symptoms include flaccid paralysis or muscle weakness and characteristic electrocardiograph (ECG) changes. Laboratory tests require special attention to blood urea nitrogen (BUN), creatinine, and serum electrolytes.

Clinical history

The patient's history constitutes the most valuable aspect in identifying elements that could incline towards hyperkalaemia. Often hyperkalaemia is discovered from the lab test results. Neurologic and cardiac symptoms predominate, although some people may exhibit only a few symptoms like generalised fatigue, weakness, and palpitations. The potential for elevated serum potassium concentration should be considered within the following clinical contexts:

- chronic or acute renal failure, particularly among patients treated with dialysis;
- trauma, burns, or rhabdomyolysis;
- use of certain drugs including potassium-sparing diuretics, potassium supplements, NSAIDs, digoxin, succinylcholine, digitalis glycoside, and beta-blockers;
- combinations of medication (for example, ACE inhibitors + spironolactone);
- Redistribution—catabolic state, metabolic acidosis (diabetic ketoacidosis).

Physical examination

Vital signs evaluation is used to determine hemodynamic instability and hyperkalaemia heart arrhythmias. Cardiac assessment can reveal bradycardia, extrasystoles, or pauses.

Laboratory studies

- *Potassium concentration:* the relationship between serum potassium concentration and symptoms is not consistent. For instance, patients with chronically raised potassium could prove asymptomatic at high serum potassium concentrations.
- *Creatinine / BUN* for kidney status evaluation.
- *Glucose* for diabetic patients.
- *Calcium* if the individual has renal failure.
- *Digoxin level* in the event that the patient is treated with that drug.
- *Venous/ arterial blood gases.*
- *Urinalysis.*
- *Aldosterone and cortisol* to check for mineralocorticoid deficiency.
- *ECG* is critical during hyperkalaemia diagnosis.

Management of hyperkalaemia

General guidelines

Significant hyperkalaemia is regarded as a medical emergency that must be treated accordingly. The treatment should be based on empirical approaches.

Principles of therapy for hyperkalaemia

Calcium antagonises hyperkalaemia by returning the excitability of the resting membrane towards normal, a mechanism that is not fully understood. This effect is demonstrably independent of the serum concentration of calcium and occurs without changing the serum concentrations of potassium.

The administration of calcium could be intravenous as calcium chloride or calcium gluconate. Calcium gluconate is preferred since calcium chloride is more likely to trigger tissue necrosis with extravasation. The recommended dose is 10 mL of a 10% solution given as intravenous push over a period of two to three minutes. The cardioprotective effect occurs within minutes, although its duration is short: between 30 minutes and an hour. The dose can be repeated five minutes in cases where no improvement is observed [29].

It is necessary to exercise caution with calcium administration in individuals with suspected digoxin toxicity since rapid calcium administration could lead to a lethal dysrhythmia [54]. It is noteworthy that the possibility of digoxin toxicity does not preclude intravenous calcium gluconate administration among patients with ECG changes that predispose hyperkalaemia, such as QRS widening and loss of P waves [54]. It is necessary to exercise caution in subjects with digoxin toxicity; period of administration should be extended from two to three minutes to a 20- to 30-minute infusion time.

Insulin and glucose

Concentrations of basal insulin are important in maintaining potassium homeostasis. In addition, insulin used at pharmacologic and physiologic doses is a beneficial tool for hyperkalaemia treatment. Insulin's hypokalemic effect remains unaffected by kidney failure or the co-administration of beta adrenergic blockers. Insulin release triggered by administration of glucose attenuates the elevation in concentration of potassium. Pre-treatment in the presence of propranolol or ESRD does not diminish this attenuation [55, 56].

There have been evaluations of the hypokalemic influences of various dosing strategies of insulin in hyperkalemic and normokalemic subjects with both impaired and normal renal function [57, 58]. In these studies, administration took the form of either continuous infusion of 10 regular insulin units bolus dosage coupled with glucose or at 5 units/kg/min dose. Either approach achieved similar efficacy and reduced the concentrations of serum potassium by over 0.5 mmol/L [59]. The insulin/glucose combination's hypokalemic effect is evident at 10 minutes after administration, and continues

for a period ranging from four to six hours [60,61].

In spite of the efficacy equivalence among several strategies of dosing for insulin, there are recommendations for bolus administration of 10 insulin units due to the ease of administration and monitoring by nursing staff. It is necessary to administer at least 25g of IV dextrose for the prevention of hypoglycaemia. There should not be exclusive administration of insulin in individuals with a history of concentrations of blood glucose in excess of 13.8 mmol/L. Administering extra glucose could elevate the concentration of serum glucose and result in a potassium-rich intracellular fluid shift into the extracellular compartment, thereby antagonising insulin's potassium-reducing effect. Hypoglycaemia is a common insulin therapy side effect for hyperkalaemia in individuals suffering from ESRD, with the incidence increasing upon administration of glucose below 40 g in spite of concomitant glucose administration.

Catecholamines

Catecholamines have an important influence upon the extrarenal regulation of potassium. Catecholamines increase Na^+-K^+ ATPase activity, which increases cellular potassium uptake. Intravenous administration of Beta2-adrenergic agonists including salbutamol and terbutaline, or through nebuliser or metered dose inhaler, decreases serum potassium by 0.5 to 1.5 mmol/L [62]. The hypokalemic effects of these agents do not depend on insulin, pH, administration route, or the concentration of serum aldosterone of the beta agonist. If using beta-adrenergic agonists with insulin, there is an observed additive effect. The serum potassium starts falling within three to five minutes after administration, with an optimal effect taking place at half an hour following intravenous administration, or one-and-a-half hours through nebuliser administration, and two hours upon administration through a metered dose inhaler [63].

The favoured form for nebulised therapy should be a preparation of concentrated salbutamol (5 mg/ml). Beta2-agonists are not suggested as monotherapy in hyperkalaemia treatment although they are a beneficial adjunct with insulin [63].

Sodium bicarbonate

Sodium bicarbonate is a common treatment for hyperkalaemia. In the medical literature, there has been a long-held belief in an inverse relationship belief between blood pH and serum potassium. The initial studies supporting this belief suggested that the potassium level rose by around 0.6 mmol/L per 0.1 mmol/L decline in pH [64]. Apparently, numerous other factors apart from pH change influence the changed direction in serum potassium. Among those factors is the acid base disturbance type (metabolic or respiratory), hyperkalaemia chronicity and acuity, and the activity of other mechanisms that are critical to potassium homeostasis maintenance.

Much of the available evidence now shows that sodium bicarbonate has little benefit in the initial management of hyperkalaemia. In one study involving hyperkalemic patients, sodium bicarbonate infusion did not reduce the concentration of serum potassium after 60 minutes [65]. Further, there was no significant reduction in serum potassium observed before four to six continuous infusion hours, and the small reduction was partly attributed to dilution [65]. The combined sodium bicarbonate administration with glucose/insulin or Beta2-agonists may provide increased efficiency.High insulin levels in blood are necessary to ensure optimal potassium shift. Hypoglycaemia occurs frequently. It is essential to monitor blood glucose [66]. Administering large amounts of hypertonic bicarbonate can precipitate volume overload and hypernatremia. The benefit of sodium bicarbonate is small, unpredictable, and late in onset. Perhaps it is better to reserve it for severe metabolic acidosis patients.

Eliminating potassium from the body

Diuretics

There have been changes in hyperkalaemia epidemiology. A reported incidence rate for severe hyperkalaemia ranged between 6% and 12% in patients exhibiting congestive cardiac failure and receiving spironolactone. Based on current evidence, a reasonable therapy choice varies from the conventionally-applied algorithm, considering what we understand of the physiology relating to this group of patients [67]. Thiazide or loop diuretics play a crucial role in the treatment of chronic hyperkalaemia by increasing the distal sodium delivery and rate of urine flow, effects which are responsible for the promotion of kaliuresis. However, their role in acute conditions is limited. To lose a substantial amount of potassium it is necessary to use doses that will likely lead to some significant natriuresis. Additionally, numerous hyperkalemic patients have kidney failure that constrains the effective employment of this strategy.

Sodium polystyrene sulfonate exchange resin

Sodium polystyrene sulfonate (SPS Resonium A®) is a cation exchange resin that acts by exchanging sodium for potassium [68]. After contact with the colon for a minimum of 30 minutes, one gram of resin binds 0.65 to 1.0 mmol of potassium, which is subsequently eliminated through faeces. Due to its lengthy transit period, the oral route is more efficacious, even though it can be given as an enema [69]. The main limitations of binding resins are delayed onset of osmotic diarrhoea (for at least two hours), maximum effect appearing four to six hours after administration and risk of intestinal necrosis [70,71]. This approach is not recommended for people with evidence of bowel ischemia or obstruction, or for patients who have had a renal transplant during the initial postoperative phase.

Other available resins include calcium polystyrene sulfonate, which is used mainly for management of hyperkalaemia in cases of renal impairment. It is indicated in all states of hyperkalaemia due to acute and chronic renal failure. It is also important to emphasize that exchange resins have clinical limitations, in that these products reduce the levels of potassium by approximately 1 mEq/L within 24 hours [72].

There are also recommendations against binding resin as monotherapy in acute hyperkalaemia treatment owing to delayed onset. Resins are useful for moderate or acute hyperkalaemia characterised by concentration of serum potassium below 6 mmol/L, or for the management of chronic hyperkalaemia. It is necessary to pair SPS resin with other agents having a more rapid action onset (like Beta2-agonists or insulin/glucose) in severe hyperkalaemia cases. Use in this manner has the potential to postpone or obviate the need for dialysis.

Dialysis

Haemodialysis is one of the most efficacious approaches for reducing serum potassium. Even though all dialysis modalities have the potential to reduce serum potassium, there are differences concerning their speed of onset. Conventional haemodialysis reduces serum potassium more quickly than continuous venovenous haemodialysis, continuous venovenous hemodiafiltration, continuous venovenous hemofiltration, or peritoneal dialysis [73]. Studies that assess removal of potassium through haemodialysis show that potassium is removable at a rate of 25 to 50 mmol/hour(although this depends on the dialysate bath composition), with a considerable reduction in concentrations of potassium by 1.3 mmol /L observable within sixty minutes of commencing therapy [73, 74].

In the course of conventional haemodialysis, ultrafiltration eliminates 15% of the potassium, while dialytic elimination is responsible for the rest. The amount of eliminated potassium varies with session duration, potassium concentration in the dialysate, dialyser permeability and size, or the prescribed ultrafiltration amount. Additionally, factors affecting the gradient of blood to dialysate potassium can alter the amount of eliminated potassium over the course of the haemodialysis session.

Follow-up after initial treatment

Following initial treatment of significant hyperkalaemia, ongoing biochemical, pharmacological, and clinical monitoring for recurrence of hyperkalaemia is a critical element in achieving its effective management.

The concentration of serum potassium must be checked at intervals of two and four hours after treatment until the possibility of recurrence has been excluded. During this time, pharmacological treatment may need to be repeated. For patients who have predisposing risk factors, or who are taking drugs that cause hyperkalaemia, more frequent monitoring of serum potassium level is needed, as well as monitoring for signs and symptoms of hyperkalaemia. For those who have recurrent hyperkalaemia, long-term treatment is very important. It is also necessary to identify and eliminate any potential adjunctive or causative factors responsible for hyperkalaemia.

Fig 1. Treatment algorithm for management of hyperkalaemia

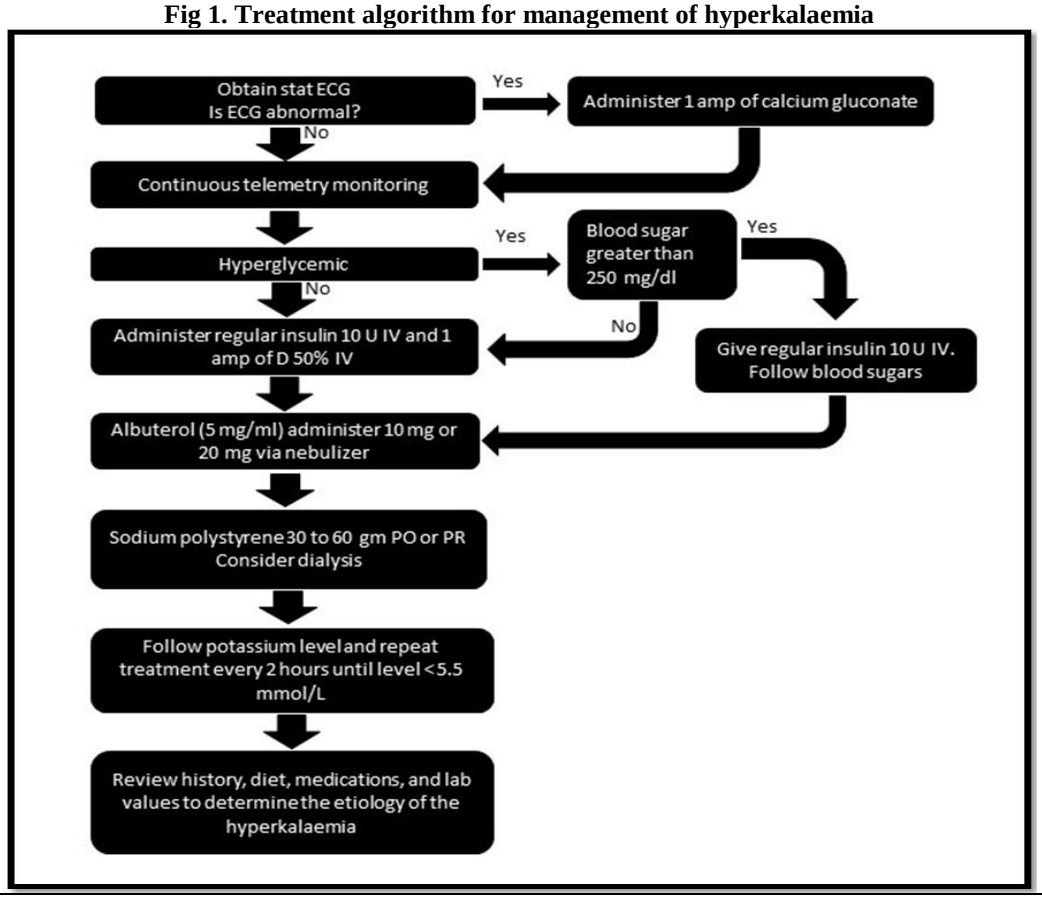

Table 1. Treatment approaches for hyperkalaemia

Step 1	Continuous electrocardiogram telemetry for serum potassium greater than 6.0 mmol/L or if ECG abnormalities are present.
Step 2	If ECG abnormalities are present, intravenous administration of 1 ampoule (10 mL of 10% solution) of calcium gluconate. Can repeat dose in 5 minutes if no improvement in ECG abnormalities.
Step 3	Administer concomitantly 10 units of regular insulin IV and 25 to 50 g of glucose if individual is not hyperglycaemic. This can be given as an infusion of 250 to 500 mL of 10% dextrose in water over 1 hour or 1 to 2 ampoules of 50% dextrose in water given as a slow push. 10 to 20 mg of concentrated salbutamol (5 mg/mL) via nebuliser.
Step 4	Remove potassium from the body. Sodium polystyrene sulfonate (if not contraindicated by presence of ileus or bowel obstruction). Give 30 to 60 g in 70% sorbitol by mouth or as a retention enema; repeat every 2 hours as needed. Dialysis may be indicated in individuals receiving renal replacement therapy or receiving renal replacement therapy or those with acute renal failure.
Step 5	Review medication list 1. Discontinue potassium administration. 2. Discontinue medications that interfere with potassium excretion.
Step 6	Review case for underlying conditions contributing to development of hyperkalaemia and correct to the degree possible.
Follow-up	Repeat the serum potassium concentration in 2 hours and as needed. Repeat steps 1 through 4 if serum potassium still greater than 6.0 mmol/L on repeat.

CONCLUSION

Data analysis suggests that polypharmacy, advanced age, and multiple medical co-morbidities are risk factors for adverse outcomes from hospitalization. When treatment involves medications associated with hyperkalaemia, patient monitoring is essential. Conventional approaches to management were effective in the management of the majority of cases in this study. More extensive research using a design with a large sample size and more detailed analysis is needed.

ACKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCES

1. Evans KJ, Greenberg A. Hyperkalemia: a review. *J Intensive Care Med*, 20(5), 2005, 272-90.
2. Sterns RH, Cox M, Feig PU, Singer I. Internal potassium balance and the control of the plasma potassium concentration. *Medicine (Baltimore)*, 60(5), 1981, 339-54.
3. Brown RS. Extrarenal potassium homeostasis. *Kidney Int*, 30(1), 1986, 116-27.
4. Clausen T, Everts ME. Regulation of the Na,K-pump in skeletal muscle. *Kidney Int*., 35(1), 1989, 1-13.
5. Bastl CP, Hayslett JP. The cellular action of aldosterone in target epithelia. *Kidney Int.*, 42(2), 1992, 250-64.
6. Panese S, Mártin RS, Virginillo M, Litardo M, Siga E, Arrizurieta E, et al. Mechanism of enhanced transcellular potassium-secretion in man with chronic renal failure. *Kidney Int*., 31(6), 1987, 1377-82.
7. Williams ME, Gervino EV, Rosa RM, Landsberg L, Young JB, Silva P, et al. Catecholamine modulation of rapid potassium shifts during exercise. *N Engl J Med*., 312(13), 1985, 823-7.
8. Adrogué HJ, Madias NE. Changes in plasma potassium concentration during acute acid-base disturbances. *Am J Med*, 71(3), 1981, 456-67.
9. Hayslett JP, Binder HJ. Mechanism of potassium adaptation. A*m J Physiol*, 243(2), 1982, F103-12.
10. Kahn T, Kaji DM, Nicolis G, Krakoff LR, Stein RM. Factors related to potassium transport in chronic stable renal disease in man. *Clin Sci Mol Med*, 4(6), 1978, 661-6.
11. Widmer B, Gerhardt RE, Harrington JT, Cohen JJ. Serum electrolyte and acid base composition. The influence of graded degrees of chronic renal failure. *Arch Intern Med*., 139(10), 1979, 1099-102.
12. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. *N Engl J Med*, 351(15), 2004, 1548-63.
13. Tran HA. Extreme hyperkalemia. *South Med J*, 98(7), 2005, 729-32.
14. Moore ML, Bailey RR. Hyperkalaemia in patients in hospital. *N Z Med J*., 102(878), 1989, 557-8.
15. Segura J, Ruilope LM. Hyperkalemia risk and treatment of heart failure. *Heart Fail Clin*., 4(4), 2008, 455-64.
16. Weisberg LS. Management of severe hyperkalemia. *Crit Care Med*, 36(12), 2008, 3246-51.

17. McCaughan D. Hazards of non-prescription potassium supplements. *Lancet*. 1(8375), 1984, 513-4.
18. Ray K, Dorman S, Watson R. Severe hyperkalaemia due to the concomitant use of salt substitutes and ACE inhibitors in hypertension: a potentially life threatening interaction. *J Hum Hypertens*, 13(10), 1999, 717-20.
19. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med*, 158(20), 1998, 2200-11.
20. Soulillou JP, Fillaudeau F, Keribin JP, Guenel J. Acute hyperkalemia risks in recipients of kidney graft cooled with Collins' solution. *Nephron*, 19(5), 1997, 301-4.
21. Perez GO, Oster JR, Pelleya R, Caralis PV, Kem DC. Hyperkalemia from single small oral doses of potassium chloride. *Nephron*, 36(4), 1984, 270-1.
22. Grossman E, Verdecchia P, Shamiss A, Angeli F, Reboldi G. Diuretic treatment of hypertension. *Diabetes Care*, 34, 2011, S313-9.
23. DeFronzo RA, Cooke CR, Goldberg M, Cox M, Myers AR, Agus ZS. Impaired renal tubular potassium secretion in systemic lupus erythematosus. *Ann Intern Med*, 86(3), 1997, 268-71.
24. Batlle DC, Arruda JA, Kurtzman NA. Hyperkalemic distal renal tubular acidosis associated with obstructive uropathy. *N Engl J Med*, 304(7), 1981, 373-80.
25. DeFronzo RA, Taufield PA, Black H, McPhedran P, Cooke CR. Impaired renal tubular potassium secretion in sickle cell disease. *Ann Intern Med*, 90(3), 1979, 310-6.
26. Perazella MA, Mahnensmith RL. Hyperkalemia in the elderly: drugs exacerbate impaired potassium homeostasis. *J Gen Intern Med*, 12(10), 1977, 646-56.
27. DeFronzo RA, Felig P, Ferrannini E, Wahren J. Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. *Am J Physiol*, 238(5), 1989, E421-7.
28. Ponce SP, Jennings AE, Madias NE, Harrington JT. Drug-induced hyperkalemia. *Medicine (Baltimore)*, 64(6), 1985, 357-70.
29. Hollander JC, Calvert JF. Hyperkalemia. *Am Fam Physician*,73(2), 2006, 283-90.
30. Alappan R, Perazella MA, Buller GK. Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med*, 124(3), 1996, 316-20.
31. White PC. Disorders of aldosterone biosynthesis and action. *N Engl J Med*, 331(4), 1994, 250-8.
32. Antoniou T, Gomes T, Mamdani MM, Yao Z, Hellings C, Garg AX, et al. Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: nested case-control study. *BMJ*, 343, 2011, d5228.
33. Velázquez H, Perazella MA, Wright FS, Ellison DH. Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med*, 119(4), 1993, 296-301.
34. Tan SY, Shapiro R, Franco R, Stockard H, Mulrow PJ. Indomethacin-induced prostaglandin inhibition with hyperkalemia. A reversible cause of hyporeninemic hypoaldosteronism. *Ann Intern Med*, 90(5), 1979, 783-5.
35. Garella S, Matarese RA. Renal effects of prostaglandins and clinical adverse effects of nonsteroidal anti-inflammatory agents. *Medicine (Baltimore)*, 63(3), 1984, 165-81.
36. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? *Arch Intern Med*, 158(1), 1988, 26-32.
37. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*, 289(13), 2003, 1652-8.
38. Bantle JP, Nath KA, Sutherland DE, Najarian JS, Ferris TF. Effects of cyclosporine on the renin-angiotensin-aldosterone system and potassium excretion in renal transplant recipients. *Arch Intern Med*, 145(3), 1985, 505-8.
39. Jain AB, Fung JJ, Todo S, Reyes J, Selby R, Irish W, et al. One thousand consecutive primary orthotopic liver transplants under FK 506: survival and adverse events. *Transplant Proc*, 27(1), 1995, 1099-104.
40. Oster JR, Singer I, Fishman LM. Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med*, 98(6), 1995, 575-86.
41. Canova CR, Fischler MP, Reinhart WH. Effect of low-molecular-weight heparin on serum potassium. *Lancet*, 349(9063), 1997, 1447-8.
42. Levesque H, Verdier S, Cailleux N, Elie-Legrand MC, Gancel A, Basuyau JP, et al. Low molecular weight heparins and hypoaldosteronism. *BMJ*, 300(6737), 1990, 1437-8.
43. Bismuth C, Gaultier M, Conso F, Efthymiou ML. Hyperkalemia in acute digitalis poisoning: prognostic significance and therapeutic implications. *Clin Toxico*, 6(2), 1973, 153-62.
44. Norgaard A, Botker HE, Klitgaard NA, Toft P. Digitalis enhances exercise-induced hyperkalaemia. *Eur J Clin Pharmacol*, 41(6), 1991, 609-11.
45. Moreno M, Murphy C, Goldsmith C. Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. *J Lab Clin Med*, 73(2), 1969, 291-8.
46. Castellino P, Bia MJ, DeFronzo RA. Adrenergic modulation of potassium metabolism in uremia. *Kidney Int*, 37(2), 1990, 793-8.
47. Lundborg P. The effect of adrenergic blockade on potassium concentrations in different conditions. *Acta Med Scand Suppl*, 672, 1983, 121-6.

48. Arthur S, Greenberg A. Hyperkalemia associated with intravenous labetalol therapy for acute hypertension in renal transplant recipients. *Clin Nephrol*, 33(6), 1990, 269-71.
49. Hamad A, Salameh M, Zihlif M, Feinfeld DA, Carvounis CP. Life-threatening hyperkalemia after intravenous labetolol injection for hypertensive emergency in a hemodialysis patient. *Am J Nephrol*, 1(3), 2001, 241-4.
50. http://iom.nationalacademies.org/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx.
51. Burrowes JD, Ramer NJ. Removal of Potassium From Tuberous Root Vegetables by Leaching. *J Ren Nutr*, 16(4), 2006, 304-11.
52. Adhiyaman V, Asghar M, Oke A, White AD, Shah IU. Nephrotoxicity in the elderly due to co-prescription of angiotensin converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs. *J R Soc Med*, 94(10), 2001, 512-4.
53. Fenton F, Smally AJ, Laut J. Hyperkalemia and digoxin toxicity in a patient with kidney failure. *Ann Emerg Med*, 28(4), 1996, 440-1.
54. Nola GT, Pope S, Harrison DC. Assessment of the synergistic relationship between serum calcium and digitalis.. *Am Heart J*, 79(4), 1970, 499-507.
55. Alvestrand A, Wahren J, Smith D, DeFronzo RA. Insulin-mediated potassium uptake is normal in uremic and healthy subjects. *Am J Physiol*, 246(2 Pt 1), 1984, E174-80.
56. Allon M, Dansby L, Shanklin N. Glucose modulation of the disposal of an acute potassium load in patients with end-stage renal disease. *Am J Med*, 94(5), 1993, 475-82.
57. Kim HJ. Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. *Nephron*, 72(3), 1996, 476-82.
58. Blumberg A, Weidmann P, Shaw S, Gnädinger M. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med*, 85(4), 1998, 507-12.
59. Evans K, Reddan DN, Szczech LA. Nondialytic management of hyperkalemia and pulmonary edema among end-stage renal disease patients: an evaluation of the evidence. *Semin Dial*, 17(1), 2004, 22-9.
60. Goldfarb S, Cox M, Singer I, Goldberg M. Acute hyperkalemia induced by hyperglycemia: hormonal mechanisms. *Ann Intern Med*, 84(4), 1976, 426-32.
61. Montoliu J, Revert L. Lethal hyperkalemia associated with severe hyperglycemia in diabetic patients with renal failure. *Am J Kidney Dis*, 5(1), 1985, 47-8.
62. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int*, 38(5), 1990, 869-72.
63. 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*, 74(8), 1997, 503-9.
64. Fulop M. Serum potassium in lactic acidosis and ketoacidosis. *N Engl J Med.*, 300(19), 1979, 1087-9.
65. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. *Am J Kidney Dis*, 28(4), 1996, 508-14.
66. Kamel KS, Wei C. Controversial issues in the treatment of hyperkalaemia. *Nephrol Dial Transplant*, 18(11), 2003, 2215-8.
67. Chapagain A, Ashman N. Hyperkalaemia in the age of aldosterone antagonism. *QJM*, 05(11), 2012, 1049-57.
68. Scherr L, Ogden DA, Mead AW, Spritz N, Rubin AL. Management of hyperkalemia with a cation-exchange resin. *N Engl J Med*, 264, 1961, 115-9.
69. Iqbal Z, Friedman EA. Preferred therapy of hyperkalemia in renal insufficiency: survey of nephrology training-program directors. *N Engl J Med*, 320(1), 1989, 60-1.
70. Flinn RB, Merrill JP, Welzant WR. Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report. *N Engl J Med*, 264, 1961, 111-5.
71. Blumberg A, Roser HW, Zehnder C, Müller-Brand J. Plasma potassium in patients with terminal renal failure during and after haemodialysis; relationship with dialytic potassium removal and total body potassium. *Nephrol Dial Transplant*, 12(8), 1997, 1629-34.
72. Parham WA, Mehdirad AA, Biermann KM, Fredman CS. Hyperkalemia revisited. *Tex Heart Inst J*, 33(1), 2006, 40-7.
73. Hou S, McElroy PA, Nootens J, Beach M. Safety and efficacy of low-potassium dialysate. *Am J Kidney Dis*, 13(2), 1989, 137-43.
74. Feig PU, Shook A, Sterns RH. Effect of potassium removal during hemodialysis on the plasma potassium concentration. *Nephron*, 7(1), 1981, 25-30.