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Original Research Article

Overview of Aetiology of Hypokalaemia in Cancer Patients: A Narrative Review

Dr. Narita Khurshid[1]*, Dr. Kazi Abdullah Arman[2], Dr. Abdullah Al Mamun Khan[3], Dr. Mehdi Faruk[4]

[1]MBBS, MD Medical Oncology, Associate Consultant, Evercare Hospital Dhaka-1229
[2]MBBS, MD, Consultant Labaid Cancer Hospital
[3]Associate Professor of Medical Oncology, Shaheed Suhrawardy Medical College, Dhaka
[4]Assistant professor, Uttara Adhunik Medical College & Hospital

***Corresponding Author:** Dr. Narita Khurshid
MBBS, MD Medical Oncology, Associate Consultant, Evercare Hospital Dhaka-1229

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Abstract: ***Introduction*:** Hypokalaemia or potassium deficiency in cancer patients is the second highest Electrolyte Disorder (ED) after Hyponatremia. Deficiency of potassium can cause sudden vital organ failure in malignancy, if it is not diagnosed and manage immediately. Additionally, there remain many risk factors related to malignancy and its treatment to developing potassium deficiency. This narrative review was conducted to document an overview of aetiology of Hypokalaemia in patients with different stage of various types of cancer. ***Aim*:** The narrative review could be informative and important in recognizing Hypokalaemia in oncology treatment and management. ***Research Question*:** What is the aetiology of developing hypokalaemia in cancer patients? ***Methodology*:** Literatures were selected for review based on inclusion and exclusion criteria. Selection was done purposively based on several outcome and information regarding potassium deficiency in cancer patients. Articles were reviewed by mainly considering the population and results of the study. Main author reviewed the papers and cross-checked with third author, and finally came to conclusion after consensus. ***Inclusion Criteria*:** a) Study on cancer patients developing hypokalaemia, b) Study on hypokalaemia as an outcome of cancer treatment and management, c) Study on mechanism of developing hypokalaemia in cancer patients, and d) Study on hypokalaemia resulting from risk factors as a consequence of cancer. ***Exclusion Criteria*:** a) Study on hypokalaemia not due to cancer treatment or management, b) Incomplete study, c) Not found in online publications/digital libraries/e-journals. ***Study Period*:** Review period was January to March 2021. ***Literature Search*:** Keyword based scientific paper search underwent through Google Scholar, PubMed and Embase. ***Results and Discussion*:** Aitiology of hypokalaemia can be grouped under four headings: a) Malignancy, itself, b) treatment of the cancer that includes chemotherapy and targeted therapies; c) concomitant drugs and d) concomitant diseases; endocrine dysfunction, toxic epidermal necrolysis, inflammatory bowel diseases among others. There are three mechanisms found to be involved which are caused by the above mentioned risk factors. They are: an inadequate potassium intake, redistribution of potassium among intra- and extracellular compartments, and potassium losses. ***Conclusion*:** Hypokalaemia in cancer patients is a life-threatening situation and increases mortality and morbidity. Recognizing and understanding the aetiology could be helpful for the clinicians, especially the oncologists to reduce the suffering and improve palliative management in cancer patients.

Keywords: Hypokalaemia, Cancer Patients, Electrolytes Disorder (ED), Chemotherapy and Targeted Therapy Induced Potassium Deficiency.

INTRODUCTION

Hypokalaemia is defined as a serum potassium level less than 3.5 milli equivalent (mEq) per litre (L). Electrolyte abnormalities are commonly associated with lethal cardiovascular emergencies. These abnormalities may cause or contribute to cardiac arrest and may hinder resuscitative efforts [1]. In some cases, therapy for life-threatening electrolyte disorders should be initiated before laboratory results become available. Nonetheless, hypokalaemia is found in 20% of

hospitalized patients [2]. The majority of these patients have serum potassium concentrations between 3.0 and 3.5 mmol per liter, but as many as one quarter have values below 3.0 mmol per liter. Unfortunately, comparable data are not available for inpatients or outpatients in Bangladesh, although alarming data has shown- a low serum potassium concentration has been found in 10 to 40 percent of patients [1]. Healthy individuals are less affected by hypokalemia, but it can be life-threatening when severe. Even mild or moderate hypokalemia increases the risks of morbidity and mortality in patients with cardiovascular disease [2]. Patients with malignancy are in higher risk of developing hypokalaemia due to the course of the illness, which remarkably increases the mortality and morbidity. Statistically, hospital inpatients develop hypokalaemia in frequent manner, 21% to be found in recent studies, of which 5.2% had the serum potassium less than 3.0 mmol/l [3]. Alarmingly, patients with leukaemia and lymphoid tumours, especially when receiving antibiotic or cytotoxic therapy, and patients with gastro-intestinal malignancy were amongst those most frequently experiencing hypokalaemia [4]. Drug and intravenous fluid administration accounted for the hypokalaemia in 56% of patients. While drug-related hypokalaemia was most commonly seen with diuretics, it was also apparent following use of steroids and insulin.

The hypokalaemia increases the mortality and morbidity among cancer patients [3]. Thus, the study of the aetiology of the disorder, potassium deficiency in cancer patients, requires proper research attention in clinical oncology.

BACKGROUND

Potassium Functioning on Molecular Level

Potassium, an electrolyte, is a mineral found in the foods we eat. Electrolytes conduct electrical impulses throughout the body. They assist in a range of essential body functions, including blood pressure, normal water balance, muscle contractions, nerve impulses, digestion, heart rhythm, pH balance (acidity and alkalinity). Our body does not produce potassium naturally. So, it's important to consume the right balance of potassium-rich foods and beverages. Healthy kidneys maintain normal potassium levels in the body because they remove excess amounts through urine [5].

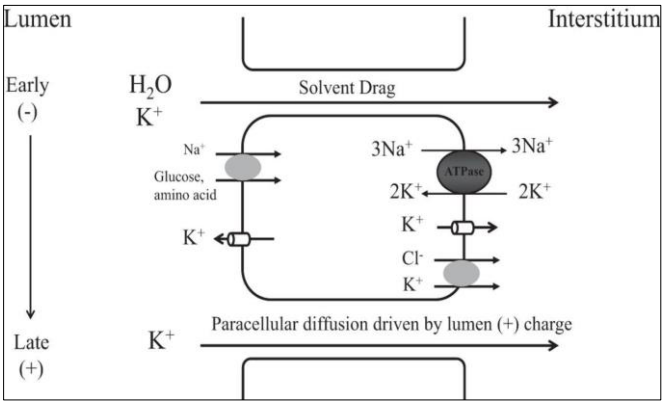


Fig. 1: Component of K^+ handling

A large component of filtered K^+ is reabsorbed by the proximal tubule primarily through the paracellular pathway driven by solvent drag. The shift in lumen potential from negative to positive in the later portions of the proximal tubule provides an additional driving force for K^+ reabsorption. On the basolateral surface, K^+ entry into the intracellular space by the Na^+-K^+-ATPase exits coupled to Cl^- via a conductive pathway. A K^+ channel on the apical surface of the proximal tubule acts to stabilize cell voltage given the depolarizing effect of Na^+-coupled glucose and amino acid reabsorption.

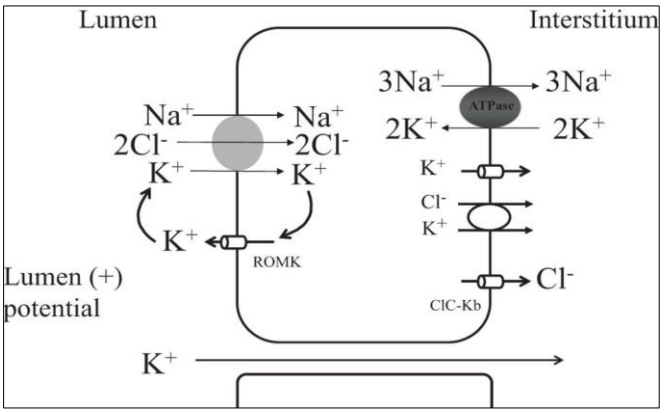


Fig. 2: Active transport of K+ through renal outer medullary potassium (ROMK) channel

The majority of filtered K^+ that escapes reabsorption in the proximal tubule is reabsorbed in the thick ascending limb by both transcellular and paracellular pathways. The transcellular pathway is an example of secondary active transport. Intracellular Na^+ is kept low by activity of the Na^+-K^+-ATPase. Luminal Na^+ enters the cell along with Cl^- and K^+ via the Na^+-K^+-Cl^- cotransporter. An adequate amount of luminal K^+ for the cotransport step is ensured by K^+ movement from the intracellular space into the lumen via the apically located renal outer medullary potassium (ROMK) channel. This recycling of K^+ leads to generation of a lumen-positive charge, providing the driving force for a second component of K^+ reabsorption through the paracellular pathway. Intracellular K^+ can also exit the basolateral membrane in cotransport with Cl^- or by way of a conductive pathway. ClC-Kb, Cl^- channel. Electrogenic secretion through the ROMK channel is the major K^+ secretory mechanism in the distal nephron. Maxi-K^+ or BK channels are a second type of channel that also mediates K^+ secretion under conditions of increased flow. In addition to stimulating maxi-K^+ channels, tubular flow also augments electrogenic K^+ secretion by diluting luminal K^+ concentration and stimulating Na^+ reabsorption through the epithelial Na^+ channel (ENaC). This stimulatory effect can be traced to a mechanosensitive property whereby shear stress increases the open probability of the ENaC channel.

The biomechanical characteristics for Na^+ and K^+ transport in the distal nephrons is ideally suited to buffer any increase in extracellular K^+ concentration following a protein-enriched meal, which is also high in K^+ content. In this setting there is an increase in glomerular filtration rate and tubular flow. High flow and increases in distal Na^+ delivery activate the maxi-K^+ channel and augment electrogenic K^+ secretion through ROMK, respectively. Increased flow also dilutes luminal K^+ concentration, keeping the gradient for K^+ secretion optimal [5, 6].

Causes of Hypokalaemia

There are over 20 clinical etiologies of hypokalaemia. It is useful to think about etiologies in three general categories: a) cellular shifts, b) extrarenal losses and c) renal losses.

A) Cellular Shifts:

Poor potassium intake, hypokalaemia periodic paralysis, metabolic alkalosis, hyperthyroidism, insulin use, beta-adrenergics (pharmacologic or intrinsic). A cellular shift of potassium from the extracellular to the intracellular compartment causes hypokalaemia. This occurs with metabolic alkalosis, with insulin or beta-agonist administration, with hyperthyroidism, and in the periodic paralysis syndromes. In general, the magnitude of the hypokalaemia that accompanies cellular shifts is modest. In healthy volunteers, a single dose of aerosolized salbuterol lowers serum potassium by 0.2-0.4 mEq/L, and this effect may persist for several hours [7].

Again, evaluation of serum potassium must consider the effects of changes in serum pH. When serum pH falls, serum potassium rises because potassium shifts from the cellular to the vascular space. When serum pH rises, serum potassium falls because potassium shifts from the vascular space into the cells. Effects of pH changes on serum potassium should be anticipated during therapy for hyperkalaemia or hypokalaemia and during any therapy that may cause changes in serum pH (e.g., treatment of diabetic ketoacidosis) [2].

In delirium tremens [9], serum potassium may decline by 1 mEq/L due to the effects of high levels of intrinsic beta-agonists (primarily epinephrine and norepinephrine). When patients with delirium tremens present with serum potassium less than 2.5 mEq/L, this is almost always due to the additive effects of other etiologies (such as vomiting, alkalosis associated with volume depletion, and hypomagnesemia). In distinction to other diseases that cause intracellular shift of potassium, the hypokalaemia seen with the periodic paralysis syndromes (hypokalaemia periodic paralysis, thyrotoxic periodic paralysis, and Andersen syndrome) may result in very low levels of serum potassium (less than 2.5 mEq/L) [9].

B) Extrarenal Loss:

Diarrhoea, vomiting, excessive sweating, plasmapheresis, dialysis. Extrarenal losses of potassium occur with vomiting and diarrhoea. The potassium content in diarrhoea is much higher than in vomitus (20-50 mEq/l vs. 5-10 mEq/L), but hypokalaemia associated with vomiting is usually much more profound than that with diarrhoea, because vomiting is much more frequently associated with metabolic alkalosis and volume depletion, which result in inappropriate renal loss of potassium. Rare extrarenal causes of hypokalaemia include excessive sweating, plasmapheresis, and dialysis [7].

C) Renal Loss:

Renal loss etiologies of hypokalaemia include renal tubular acidosis, salt losing nephropathies, Bartter syndrome, and Gitelman syndrome; states associated with delivery of non-resorbable anions to the distal nephron (such as ketoacids, bicarbonate, toluene, and penicillins); states of excess mineralocorticoids (Conn's syndrome, Cushing's syndrome, corticosteroid administration); hypomagnesemia; and certain drugs (diuretics, amphotericin, and platinum) [7, 8].

Mechanism of Hypokalaemia Leading to Vital Organ Failure:

The major consequences of severe hypokalaemia result from its effects on nerves and muscles (including cardiac muscle). The myocardium is extremely sensitive to the effects of hypokalaemia, particularly if the patient has coronary artery disease or is taking a digitalis derivative. Hypokalaemia can produce ECG changes such as U waves, T-wave flattening, and arrhythmias (especially if the patient is taking digoxin), particularly ventricular arrhythmias. Pulseless electrical activity or asystole may also develop [2]. Although hypokalaemia may be accompanied by electrocardiographic abnormalities (depression of ST segments, loss of T wave amplitude, and increase in U wave amplitude), the degree of hypokalaemia that is associated with these changes is quite variable. Thus, as opposed to hyperkalaemia, T-wave changes seen on the 12-lead electrocardiogram (EKG) do not often guide the decision about treatment of hypokalaemia. However, rhythm monitoring may be useful to detect arrhythmias associated with hypokalaemia. In patients with severe hypokalaemia (potassium less than 2.5 mEq/L), the presence of serious arrhythmias (such as ventricular tachycardia or rapid atrial fibrillation) is often used to assist with decisions about the rapidity of treatment. The patients, in whom one of the periodic paralysis syndromes is suspected, the EKG may be useful diagnostically, since a prolonged QT interval is characteristically seen in Andersen syndrome and not seen in hypokalaemia periodic paralysis or thyrotoxic periodic paralysis. In that case, thyroid function testing is useful for those patients with suspected thyrotoxic periodic paralysis [8]. The magnitude of the potassium gradient across cell membranes determines excitability of nerve and muscle cells, including the myocardium.

METHODOLOGY

The narrative review was conducted to summarize the aetiology of hypokalaemia among cancer patients. The studies were selected mainly based on the risk factors in relation to the development of hypokalaemia where the study population were cancer patients or their treatment/management research including cause-effect outcome among patients with tumour/malignancy. The purposive literature search through three central online providers were used for the review. The keywords were hypokalaemia and cancer patients with the chemotherapy or outcomes such as electrolytes disorders (ED), diarrhoea, vomiting, acute kidney injury, malnutrition, delirium etc.

The first author railed all the study papers for review in the line of same population (cancer patients), risk factors (aetiology of hypokalaemia) and outcome (hypokalaemia) by keywords. Then the list became shorter by screening after reading the titles, then the abstract, and finally the full text. The review was cross-checked by the second and third author. Finally, the results were discussed among all the authors to finalize the number of the literatures, the strengths and limitation, and concluded with the following findings.

Inclusion Criteria:

a. Study on cancer patients developing hypokalaemia,
b. Study on hypokalaemia as an outcome of cancer treatment and management,
c. Study on mechanism of developing hypokalaemia in cancer patients,
d. Study on hypokalaemia resulting from risk factors as a consequence of cancer.

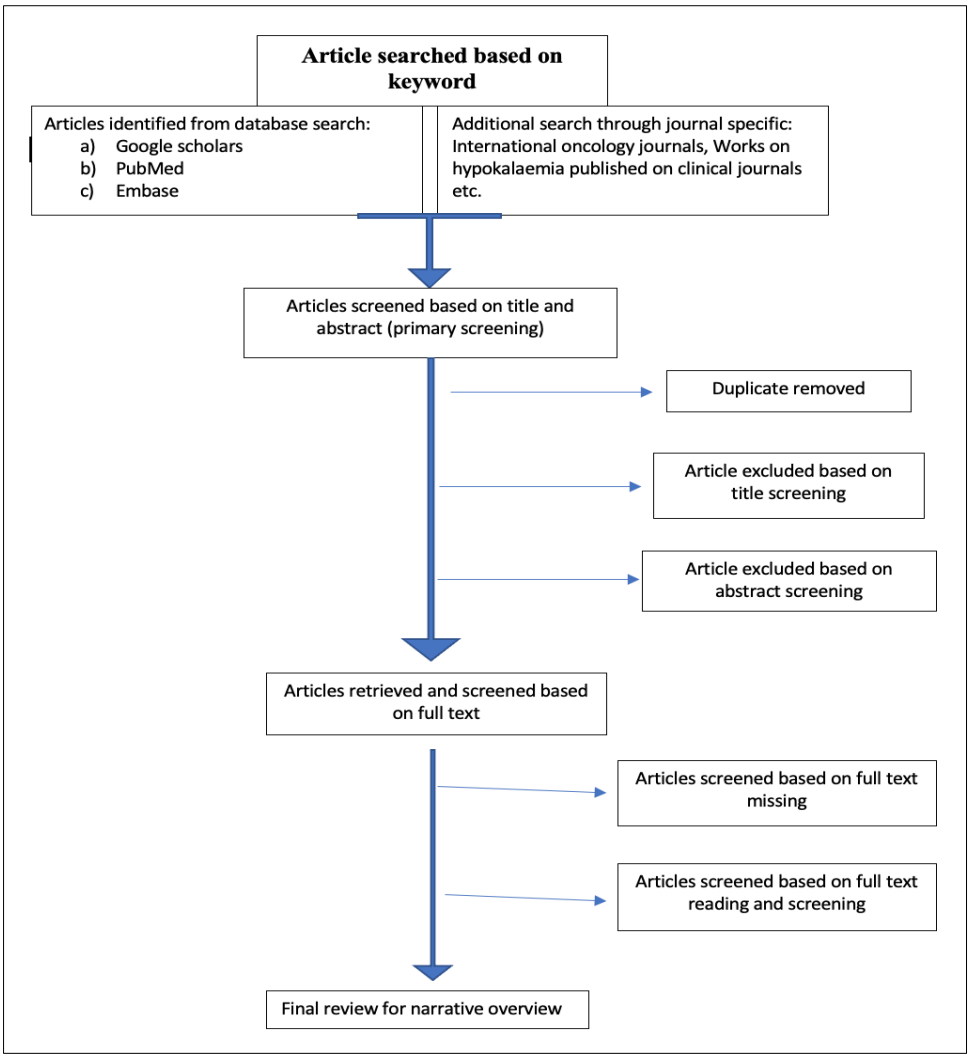
Exclusion Criteria:

a. Incomplete study
b. Not found in online publications/digital libraries/e-journals.

Study Period and Materials:

Review period was January 2021 to March 2021 with continuous writing of the paper until April 2021. All the studies found fulfilling the criteria was reviewed for this narrative scientific documentation.

Literature Search: Keyword based scientific paper search underwent through Google Scholar, PubMed and Embase.



[# Studies selected from last decade (not conducted before 2010), several articles on basic preclinical research are taken as landmark studies.]

Flowchart: Inclusion of studies for the narrative review.

Ethical Consideration:

The review was initiated from the interest of clinical oncology. All the study was selected from online resources. The review was a desk research done by the team of the authors; thus no ethical clearance was needed.

RESULTS

In this review, reliable evidence from 2010 to 2020 were scrutinized and synthesized to answer the question: "What is the aetiology of developing hypokalaemia in cancer patients?". Special causes for developing hypokalaemia in cancer patients are as follows:

Cancer Itself

In small-cell lung cancer, amongst the important causes of low potassium levels in blood are adrenocorticotropic hormone (ACTH)-secreting tumours. Ectopic Cushing's syndrome, secondary to lung cancer, is a rare occurrence with poor prognosis, but it may manifest with severe hypokalaemia (alongside hyperglycaemia and muscle weakness). A proper control of severe hypercortisolism prior to administering systemic chemotherapy may result in prolonged survival [44].

Development of Hypomagnesaemia Leading to Hypokalaemia

Magnesium (Mg^{++}) is the second most abundant divalent cation in the human body [10]. It is mainly stored in bone, muscle, and soft tissues, and is important for neurotransmission, protein, and DNA synthesis, hormone-receptor interaction. Its normal serum concentration ranges between 1.6 and 2.6 mg/dL (0.65-1.07 mmol/L), and its homeostasis depends on intestinal absorption and renal excretion. In the kidney, transient receptor potential cation channel, subfamily

M, member 6 (TRPM6), a Mg^{++} channel located in the apical cellular membrane of the thick ascending limb of Henle's loop and distal convoluted tubule, and exerts the rate-limiting step for Mg tubular transport. The activity of TRPM6 is regulated by the epidermal growth factor (EGF) and its receptor (EGFR) [14, 15]. As TRPM6 and EGF/EGFR are mainly expressed in the distal convoluted tubule, this segment represents the main site of regulation of urinary Mg excretion. Mild hypomagnesemia can be pauci-symptomatic, whereas a severe disorder can represent a life-threatening condition. Symptoms involve cardiovascular system, with electrocardiographic alterations (prolonged QT interval), and the neuromuscular system with tremor, paraesthesia, tetany, spasms, and seizures). Hypomagnesemia is also associated with reduced release and activity of parathyroid hormone (PTH) and reduced synthesis of active vitamin D and its receptors. In hospitalized cancer patients, hypomagnesemia (Mg < 1.5 mg/dL) has a prevalence around 17 % although antineoplastic drugs can increase this figure (e.g., up to 90% with cisplatin) [16, 17].

Platinum-derived agents (Chemotherapeutic agents) can induce hypokalaemia due to renal K wasting secondary to hypomagnesemia. The incidence of cisplatin-related hypokalaemia is around 27% [16, 18]. Intracellular magnesium depletion reverts inactivation of voltage-dependent renal outer medulla K channels (ROMK), thus increasing kaliuresis. Increased distal Na delivery or elevated aldosterone levels are also required for exacerbating K wasting [19]. Hypomagnesemia, by upregulating ROMK activity with ensuing potassium loss, is also involved in anti-EGFR MoAbs-induced hypokalaemia [19], Potassium supplementation may fail to correct hypokalaemia until hypomagnesemia is corrected.

Hypomagnesemia is the most frequent electrolyte alteration related to its cumulative dose. Hypomagnesemia is associated with shorter survival [16], and its incidence ranges between 56 and 90% of patients receiving cisplatin, being lower with carboplatin [4-20]. It is mainly related to an impaired Mg reabsorption in the proximal tubule [21]. However, cisplatin was shown to downregulate the TRPM6/EGF pathway resulting in Mg loss [22], and patients receiving platinum can develop persistent distal tubular dysfunction with a Gitelman-like syndrome, characterized by hypocalciuria, hypomagnesemia and hypokalaemic metabolic alkalosis [23].

In particular, among the platinum-derived drugs, cisplatin-induced hyponatremia occurred in 50% of the patients after a median critical dose of 195 mg at cycle 2, while higher cumulative doses had to be administered to observe hypokalaemia (560 mg at cycle 7). Median critical doses for development of hypomagnesemia and hypocalcemia in 50% of the patients were 160 mg and 240 mg at cycle 2 and 3, respectively, supporting the concept of a lower dose required to induce hypomagnesemia versus other ion disorders [16].

Low magnesium due to: a) Gastrointestinal: Diarrhoea, pancreatitis, irritable bowel disease, bowel resection, protein-calori malnutrition (PEM), total parenteral nutrition, bowel fistula, b) Renal: Post obstructive diuresis, post-acute tubular necrosis, renal transplantation, interstitial nephropathy, Bartter syndrome, Gitelman's syndrome, c) Medications: Proton pump inhibitors, corticosteroids, laxatives, loop and thiazide diuretics, foscarnet, digoxin, amphotericin B, colchicines, theophylline, macrolide antibiotics, petamidine, tobramycin, amikacin, tacrolimus, d) Chemotherapeutic agents: Aminoglycosides (gentamicin, streptomycin), cyclosporine, cisplatin, carboplatin, cetuximab, panitumumab, e) Other: Burns, alcoholism, diabetes: Serum hypomagnesemia is frequently observed in more than 10% of hospitalized patients, and occurrences can be as high as 65% in patients in intensive care. Patients at particularly high risk include those with leukaemia who are receiving arsenic trioxide or cisplatin. In particular, patients with acute promyelocytic leukaemia who receive arsenic trioxide as part of induction therapy are at high risk for hypomagnesemia, which can subsequently cause an increased risk for QT prolongation and possible progression to torsade de pointes. Arsenic trioxide itself can cause QT interval prolongation and lead to complete atrioventricular block and ultimately death. For these patients, it is recommended that they maintain serum potassium and Mg levels at or above 4 mEq/dL and 1.8 mg/dL, respectively. [19].

Antineoplastic Agents

A series of electrolyte derangements can develop during treatment with anti-cancer drugs. While some of these alterations may be paraneoplastic [10], in many cases specific pharmacodynamic mechanisms can be identified impacting on fluid and electrolyte metabolism. Besides the possible occurrence of acute kidney injury, proteinuria, and hypertension, [11] several antineoplastic agents can affect electrolytes tubular handling, as well as urinary water excretion by interfering with antidiuretic hormone (ADH). Chemotherapeutic agents may induce serum K^+ derangements mainly through alterations of renal tubular transport [4]. Hypokalaemia (K < 3.5 mmol/L) prevalence is around 12% in cancer population patients, [12] these figures increase between 43% and 64% in acute leukaemia [13].

Alkylating Agents

Ifosfamide (especially when combined with cisplatin) may induce hypokalaemia as a consequence of proximal or distal tubular acidosis, or acquired FS. Ifosfamide enters proximal tubular cells through organic cation transporter 2 and, after metabolization to chloroacetaldehyde, induces glutathione depletion and lipid peroxidation [24, 25]. Bendamustine, another chemotherapeutic agent designed to have both alkylating and antimetabolite properties, can induce hypokalaemia

(severe hypokalaemia in around 5%) through a distal tubulopathy (acquired Gitelman syndrome) and a mild diuretic effect [23-26]. Special attention should be given to patients with pre-existing hypokalaemia and if the cumulative dose of Bendamustine exceeds 1,080 mg/m2 in the chemotherapy scheme [23].

Antimetabolites:

Methotrexate (at a dose of 12 g/m2) can induce severe hypokalaemia, as observed in a patient with transient hypokalaemic tetraparesis occurring after intravenous high-dose administration [36]. Azacytidine (75 mg/m2/day administered subcutaneously or intravenously, days 1–7 of each 28-day cycle for 6 cycles) may also induce hypokalaemia and hypophosphatemia; potassium depletion can persist for weeks after stopping the drug, and necessitates prolonged parenteral supplementation [37].

Target Therapies for Carcinoma Treatment

Treatment with MoAbs and Target Therapies can affect potassium metabolism. Cetuximab and other anti-EGFR agents decrease potassium levels through an impairment in magnesium balance [27]. Cetuximab increased 6 times the risk of grade 3/4 hypomagnesemia (S. Mg between 0.7-0.9 or <0.7mg/dl, respectively) and grade 3/4 hypokalaemia [14-28]. The longer half-life and higher affinity of panitumumab for EGFR, as well as the overexpression of EGFR, are responsible for a high incidence of grade 3/4 hypomagnesemia and hypokalaemia in colorectal cancer patients [27]. Patients treated with cetuximab 400 mg/m2 at first dose and 250 mg/m2 weekly (or 500 mg/m2 every 2 weeks) or panitumumab 6 mg/kg (or 9 mg/kg according to the tumor types) developed hypomagnesemia and hypokalaemia [27]. Compared to cetuximab and panitumumab, zalutumumab is associated with less hypomagnesemia and hypokalaemia [19-28]. A recent phase 2 trial showed 5.9% incidence of hypomagnesemia when Cetuximab and Irinotecan were co-administered [29]. Hypomagnesemia, by upregulating ROMK activity with ensuing potassium loss, is also involved in anti-EGFR MoAbs-induced hypokalaemia [19]. Magnesium supplementation should be considered in patients undergoing treatment with Anti-EGFR MoAbs. Some authors suggest empirically prophylactic administration of Mg at the beginning of treatment [10], and oral preparations are preferred in mild hypomagnesemia, while intravenous administration for severe depletion.

Finally, a special emphasis must be given to various target therapy drugs causing diarrhoea [30], a mechanism leading to a combination of electrolyte derangements including hypokalaemia, hypomagnesemia, hypocalcemia, hypophosphatemia, normal anion gap (hyperchloremic) metabolic acidosis due to bicarbonate loss, and severe hypovolemia [31-34]. Target therapy, and in general chemotherapy, can cause nausea and vomiting. Excessive vomiting, especially over a prolonged period of time, leads to hypovolemia and hyperchloremic metabolic alkalosis due to loss of chloride and hydrogen ions associated with hypokalaemia and hypomagnesemia [35].

Miscellaneous

Antiandrogens

Abiraterone inhibits both testicular and extra-testicular androgen synthesis by inhibiting 17α- hydroxylase and 17–20 liase resulting in decreased testosterone levels. The inhibition of 17α-hydroxylase leads to the accumulation of upstream mineralocorticoids that increase epithelial Na channel and the voltage-dependent ROMK activities in the distal nephron, resulting in increased cortical collecting duct potassium secretion and ensuing hypokalaemia [38]. The incidence of all-grade hypokalaemia related to abiraterone (at a standard dose of 1,000 mg/day) ranges between 16.6 and 18% and between 2.6 and 4.4% when grade 3/4 hypokalaemia (less than 3.0 mmol/L) is considered, and occurs after 2–4 weeks from the beginning of therapy [20, 38]. Symptoms associated with mineralocorticoid excess and hypokalaemia are managed by co-administration of low-dose prednisone, potassium chloride supplementation and/or a mineralocorticoid antagonist.

Nitrosoureas

Streptozocin has a greater nephrotoxicity profile than other molecules, such as Carmustine and Lomustine. These drugs may induce renal toxicity through interstitial nephritis and tubular atrophy, resulting in Fanconi syndrome [39].

Halichondrin B Analogue:

Eribuline mesylate, a nontaxane inhibitor of microtubule dynamics has been associated with hypophosphatemia but also with hyponatremia, hypomagnesemia, and hypokalaemia (3–10%) [40, 41].

Kadcyla/Ado-Trastuzumab: also causes low potassium in patients of breast cancer [42].

White Blood Cell Count:

Low potassium levels and low white blood cell counts can occur simultaneously or independently due to the same condition or treatment approach. Low levels of white blood cells, known as neutropenia, can be caused by chemotherapy treatment or infection due to impaired immunity, according to the University of California Davis. Once our body develops

low numbers of white blood cells, we can develop secondary infections that impair the absorption of nutrients and the body's ability to maintain normal potassium levels [43].

Malignancy is Common in Older Age Groups:

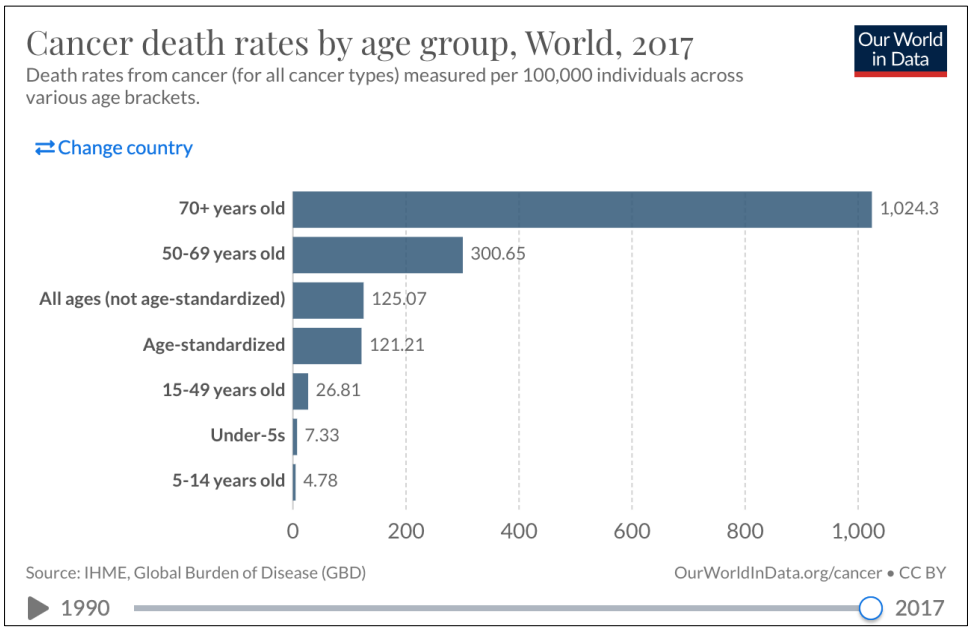


Figure 3: Global Death by age group. Sources: Our world in Data [1]

AKI is also prevalent among senior citizens. This AKI leads to low potassium in aged cancer patients. AKI in the elderly is associated with prolonged hospitalization, increased risk of transfer to an intensive care unit (ICU), subsequent institutionalization and increased short-term and long-term mortality. In addition, advanced age appears to be a risk factor for poor renal recovery from AKI, because a higher proportion of elderly AKI patients develop chronic kidney disease (CKD) or end-stage renal disease (ESRD). Dyskalemia was the most common electrolyte imbalance (43%), followed by dysnatremia (31%), hypomagnesemia (9%), hypophosphatemia (7%) and dyscalcemia (4%) (47).

Cancer and Malnutrition Are Well Established

The percentage of patients with malnutrition is particularly high for gastrointestinal and head and neck cancers. It is well accepted that enteral nutrition represents the most favourable nutritional approach because it can reduce hospital stays and medical complication. However, RS can occur as a result of the reintroduction of nutrients in patients with severe malnutrition or in starved patients on either ETF or TPN. In fact, it is well known that glucose levels decline with starvation or under conditions of carbohydrate restriction. Consequently, non-carbohydrate sources (muscle proteins) are metabolized into glucose. In addition, in the hepatocytes, fatty acid oxidation can generate ketone bodies via the Krebs cycle. Under this condition, there is significant depletion of potassium, phosphate and magnesium, as well as losses of body fat and protein mass. However, a series of homeostatic mechanisms can maintain the concentrations of these ions at normal levels. During refeeding in great quantities, when rapid increase in serum insulin occurs, the movement of extracellular potassium into the intracellular compartment can result in a dangerous decrease in potassium levels. Symptoms occur when the changes in serum electrolytes affect the cell membrane potential. Hypokalaemia could be considered an early sign of RS, and it must be promptly corrected. To reduce the risk of developing RS, both enteral and parenteral feeding should be started at a reduced calorie rate [46].

Refeeding Syndrome (RS)

It is a common condition occurring in patients with severe malnutrition. RS is associated with an increased risk of clinical complications and mortality.RS is characterized by electrolyte disorders, such as hypophosphatemia, acute vitamin B1 deficiency, volume overload, cardiac insufficiency and hyperglycaemia. Hypokalaemia could be a complication associated with refeeding in patients with cancer. Hypokalaemia was present in the early stages of high-calorie refeeding. Significant weight loss (~20%) was found in these patients. In the patients receiving artificial nutrition, lower levels of potassium and total protein were found compared with those who were fed orally ($p=0.03$ for potassium and 0.02 for protein, respectively). Patients on enteral tube feeding had a higher caloric intake compared with those who were fed orally

[1] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018. http://ghdx.healthdata.org/gbd-results-tool.

(25±5 kcal/kg/day vs. 10±2 kcal/kg/day) [47]. Potassium and magnesium become depleted during starvation. Successively, during refeeding, when these electrolytes enter cells, their serum levels further decline. Electrolytes disorders develop during the early phase of refeeding.

COVID 19

Although no definitive cause has been determined, one leading theory is that COVID 19 infection is triggered by binding of the spike protein of the virus to angiotensin converting enzyme 2, resulting in disordered renin-angiotensin system activity due to reduced counter activity of ACE 2. This leads to increased reabsorption of sodium and water, thereby increasing blood pressure and excretion of potassium.((((48))))

DISCUSSION

Cancer patients suffer from hypokalemea from the pathology of the malignancy itself and also from adverse effects of treatment. Bowel infiltration, obstruction, tumours producing ACTH, cortisol, mineralocorticoid or kidney damage in multiple myeloma can lead to low potassium. Platinum group of chemotherapy, antimetabolites specially Methotrexate, alkylating agents, anti-androgens and anti EGFR targeted therapies as well as monoclonal antibodies like ado-trastuzumab are mainly responsible for hypokalemea. So an oncologist must keep in mind the importance to follow up on serum electrolytes of the patients receiving these anti-cancer medications, before it gets life threatening. Carcinoma lung and GIT patients need special attention regarding this matter. Patients with hypomagnesemia and neutropenia should also be followed up with serum potassium level. S. potassium should be regularly checked in patients who have started on feeding after a period of starvation. Besides all the above factors, detailed history must be taken regarding covid, diabetic and thyroid disorders and regarding current use of antibiotics and diuretics.

Strengths and Limitations:

The Strength of the Study:

It is the pioneer of narrative review in Bangladeshi context, the study accumulates all the risk factors explaining the mechanism of the development of hypokalaemia and two authors of the author's team practices clinical oncology which provides the knowledge of the review from worldwide research to be translated in real life setting.

There Are Some Limitations of This Study:

First, the small number of included studies. Although we actually used a relatively broad search strategy, but when narrowed down based on the inclusion criteria, only purposively studies were taken into consideration. Second, the study methods were not analyzed. Third, only online was the source of studies. The literary works, which is not on digital library or on e-journals, was not considered, which could raise bias. Fourth, the time period of the study was limited.

CONCLUSION

Hypokalaemia is a life threatening yet preventable medical condition among cancer patients. The clinicians in oncology practice needs to be more knowledgeable about the potassium deficiency and hypokalaemia led consequences. Aiming so, the importance of timely detection of hypokalaemia and its mechanism with health consequence among cancer patients needs adequate attention from the care givers. Thereby the aetiology of the electrolytes disorder (ED), especially the hypokalaemia gets prioritized attention and remedies improving both curative and palliative care for patients with cancers.

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