Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences (IJMHRS), 2023, 12(10): 17-25

Hyponatremia and Hypokalemia Prevalence in Tuberculosis Patients Receiving Anti-tuberculosis Drugs in a Teaching Hospital

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Received: 12-October-2023, Manuscript No. ijmrhs-23-116394; **Editor assigned:** 13-October-2023, PreQC No. ijmrhs-23-116394 (PQ); **Reviewed:** 20-October-2023, QC No. ijmrhs-23-116394(Q); **Revised:** 25-October-2023, Manuscript No. ijmrhs-23-116394(R); **Published:** 31-October-2023, **J-invoice:** J-116394

ABSTRACT

Summary: *Study is conducted on tuberculosis patients admitted to a teaching hospital and deals with serum electrolytes profile analysis. Study shows prevalence of hyponatremia (56.2%) and hypokalemia (28.4%) in tuberculosis patients receiving anti-tubercular therapy.* ***Background:*** *Tuberculosis is a contagious chronic disease caused by mycobacterium tuberculosis affecting millions of people worldwide. Although primarily known impact on respiratory system, tuberculosis can lead to systemic effects including serum electrolytes imbalances.* ***Objective:*** *Aim of the study is to analyze serum sodium and potassium concentrations of tuberculosis patients on anti-tubercular therapy in a teaching hospital to evaluate their imbalances.* ***Patients and Procedures:*** *The study is conducted on 169 patients of Pulmonary Tuberculosis (PTB) in the Department of Pulmonology, Khyber teaching hospital, Peshawar from January 2018 to June 2022. The patients were going through anti-tubercular therapy. Demographics and laboratory tests were collected from the patient's hospital profile and analysis was done through GNU Project Statistical Programing Platform (GNU PSPP). Laboratory tests were performed during their stay at hospital.* ***Results:*** *The mean age was 46.29 ± 19.91 years and 51.5% of the patients were female. The mean serum sodium concentration was 133.31 ± 7.93 mmol/L and mean serum potassium concentration was 3.93 ± 0.87 mmol/L. Prevalence of hyponatremia and hypokalemia were recorded as 56.2% and 28.4% respectively. No statistically significant correlation found between variables with no statistically significant value of p.* ***Conclusion:*** *There is decrease in the level of serum sodium and potassium concentrations in tuberculosis patients.*

Keywords: Hyponatremia, Hypokalemia, Tuberculosis, Electrolyte analysis

INTRODUCTION

Electrolytes are essential for the basic life functions. Essential electrolytes comprise of sodium, potassium, chloride, calcium, magnesium and others. Food and fluids we take are the sources of electrolytes [1]. The electrolytes imbalance disturbs normal physiologies and can progress to serious life complexities1.

Sodium a basic ion is present in Extracellular Fluid (ECF), maintains ECF volume and also regulates cellular membrane potential. Sodium and potassium are exchanged across the cell membranes by active transport through Sodium-Potassium ATPase pump. Kidneys are the site of sodium regulation and in proximal tubule of nephron the major part of sodium is reabsorbed. Sodium transport is controlled by aldosterone and it occurs through sodium-chloride symporters [2].

Hyponatremia is the most frequent and common electrolyte disorder among the electrolyte imbalances. Serum sodium level below 135 mmol/L is considered hyponatremia and manifestations associated with hyponatremia include nausea, confusion, disorientation, headaches and delirium [3]. Serum sodium level above 145 mmol/L is considered hypernatremia and manifestations include unrest, tachypnea and sleeplessness. Rapidly correcting sodium imbalance could present with severe consequences like Osmotic Demyelination Syndrome (ODS) and cerebral edema. Malnutrition and long-lasting alcohol abuse are some other variables that can contribute to ODS development [4].

Hyponatremia is regarded a common electrolyte irregularity and in seriously ill hospitalized patient hyponatremia must be taken into consideration. The frequency of mild hyponatremia is estimated as 15%-30% and its severe form as 1%-4% in hospitalized patients [5].

Hyponatremia generally occurs as a result of secondary water retention to mismatch of absorption of oral or intravenous water with water excretion. Noticeable depletion of circulating volume cause release of Antidiuretic Hormone (ADH) non-osmotically and the SIADH (Syndrome of Inappropriate ADH Secretion) are the two disturbances in which antidiuretic hormone release is not subdued in spite of decrease in osmolality of plasma [6].

Hyponatremia has two familiar causes [7]. SIADH diagnosis is constituted by excluding other etiology of hyponatremia. SIADH is reported in many clinical scenarios like CNS disorders (stroke, trauma and demyelinating or inflammatory diseases), malignancies (mediastinal, extrathoracic and pulmonary tumors), pulmonary diseases (infections, positive-pressure ventilation and acute respiratory failure), drugs (phenothiazines, prostaglandin-synthesis inhibitors, desmopressin, tricyclics antidepressants and serotonin-reuptake inhibitors [7,8].

Tuberculosis can induce hyponatremia by means of a number of mechanisms containing its local invasion to the adrenal glands [9,10], local invasion to pituitary gland or hypothalamus [11,12], Tuberculous meningitis [13,14] and via pulmonary infection to secrete inappropriate antidiuretic hormone [15,16].

Potassium ion is present primarily inside the cell. Sodium-potassium ATPase pump is mainly accountable for homeostasis regulation between sodium and potassium ions, which pumps in potassium to cell in exchange of sodium, which moves out. Potassium filtration occurs at glomerulus and reabsorption of potassium takes place at PCT (Proximal Convoluted Tubule) and LOH (Loop of Henle) [17]. At distal convoluted tubule of nephron secretion of Potassium takes place and is increased by aldosterone hormone. Potassium is also secreted by potassium-chloride cotransporters and potassium channels present at the apical tubular membrane [17].

Serum potassium level below 3.5 mmol/L is considered hypokalemia. Fatigue, muscle twitching and weakness are few features of hypokalemia. Hypokalemic paralysis is systemic fatigue of body that could be sporadic or hereditary either [18]. Serum potassium concentration greater than 5.2 mmol/L is considered hyperkalemia. Muscle weakness, muscle cramps, arrhythmias, myoglobinuria and rhabdomyolysis are the clinical features of hyperkalemia. Potassium imbalances may be caused by kidneys to excrete potassium, the failure of mechanisms to move it from the circulation into the cells or combination of both factors. A rare entity called severe hypokalemia is a known sign of miliary or disseminated TB and its relation is understood poorly. Potassium imbalance may occur by dysregulation of antidiuretic hormone (SIADH) during tuberculosis and anti-tuberculotic drugs usage. Certain anti-tubercular drugs, specifically some second-line drugs that are used in the treatment of drug-resistant TB, can have negative effects on electrolyte balance and kidneys [19].

Chloride is present in ECF and its serum levels are regulated predominantly by the kidneys. Chloride filtered by glomerulus of nephrons, is mostly reabsorbed by both PCT (Proximal Convoluted Tubule) and DCT (Distal Convoluted Tubule) by active and passive transport. PCT has major part in the reabsorption of Chloride. Low chloride levels in the blood by the level of 96 mmol/L is known as hypochloremia and hyperchloremia refers to high chloride levels in the blood above the level of 106 mmol/L. chloride imbalance often occurs in association with other electrolytes [20].

Patients with chronic or subacute tuberculosis may present with nocturnal sweating, pyrexia, shivering, and dysfunction of one or more organs. Tuberculosis could be linked with Electrolytes disturbances [19].

AIMS OF STUDY

Aim of study was to find the prevalence of electrolyte imbalances in tuberculosis patients.

PATIENTS AND PROCEDURES

Study Design and Participants

Patients diagnosed with tuberculosis who were admitted to ward of Pulmonology, Khyber teaching hospital, Peshawar, Pakistan from January 2018 to June 2022 were evaluated prospectively. Demographic and characteristic laboratory tests were recorded from the hospital records of patients' charts. The patients whose demographic and laboratory characteristics tests were not present were excluded from the studies. 169 patients were included in the study.

Inclusion and Exclusion Criteria

Patients of all ages with minimum age of 12 and maximum of 90 years were included in the study. Patients irrespective of their gender were included in the study. Patients whose demographic and laboratory characteristics tests were not present were excluded from the study. A patient having data available of all the three studied electrolytes i.e., sodium, potassium and chloride was included in the study.

Statistics

Data was assembled to analyze the laboratory characteristics tests of tuberculosis patients who present with electrolyte imbalances or not. The data was compared and analyzed with the help of GNU Project Statistical Programing Platform (GNU PSPP). The significant consideration for P value was less than 0.05. Data was analyzed and written with the help of mean, percentage and standard deviation. Tests were performed to check the distribution of quantitative data. The variables were mostly abnormally distributed and Kruskal-Wallis, spearman correlation and Mann-Whitney U tests were performed.

RESULTS

The mean age was 46.29 ± 19.91 and 51.5% of the patients were female. The mean serum sodium concentration was 133.31 mmol/L ± 7.93 mmol/L. The mean serum potassium and chloride concentrations were 3.93 mmol/L ± 0.87 mmol/L and 100.40 mmol/L ± 8.51 mmol/L respectively. Analyzing the sodium level 56.2% of patients showed hyponatremia, 41.4% were normal and 2.4% showed hypernatremia. Analyzing the potassium level 28.4% of patients showed hypokalemia, 66.9% were normal and 4.7% showed hyperkalemia. Analyzing the chloride level 24.9% of patients showed hypochloremia, 55% were normal and 20.1% showed hyperchloremia. No statistically significant correlation found between variables with no statistically significant value of p.

DISCUSSION

According to the findings of our study the frequency of hyponatremia, hypokalemia and hypochloremia come out as 56.2%, 28.4%, and 24.9% respectively. Additionally, prevalence of hypernatremia, hyperkalemia and hyperchloremia obtained as 2.4%, 4.7%, and 21.1% respectively. 24.9% hypochloremia and 21.1% hyperchloremia prevalence cannot be ignored in our study because no considerable amount of research data is available related to chloride abnormalities in tuberculosis patients. The variables age and gender were seen having no relation with the electrolyte imbalances in tuberculosis patients. There was no significant relation between one electrolyte imbalances with another (Table 1 and 2).

Table 1 Frequency of electrolytes level to age

Age	Sodium level			Potassium level			Chloride level			Total
	<135	135-145	>145	<3.5	3.5-5.2	>5.2	<96	96-105	>105	

<30	28	24	0	17	34	1	12	30	10	52
30-60	50	31	1	22	57	3	21	46	15	82
>60	17	15	3	9	22	4	9	17	9	35
Total	95	70	4	48	113	8	42	93	34	169
Note: < shows "less than" and > shows "more than". Age in years and electrolytes level in mmol/L										

Table 2 Frequency of electrolytes level to gender

Gender	Sodium level			Potassium level			Chloride level			Total
	<135	135-145	>145	<3.5	3.5-5.2	>5.2	<96	96-105	>105	
Female	46	39	2	29	55	3	19	50	18	87
Male	49	31	2	19	58	5	23	43	16	82
Total	95	70	4	48	113	8	42	93	34	169
Note: < shows "less than" and > shows "more than". Electrolytes level in mmol/L										

In previous studies of hyponatremia prevalence among admitted patients, particularly the inpatients of respiratory wards, was documented in a range of (2.48%-40%) [21]. Hyponatremia prevalence of 51% was reported by Jonaidi Jafari N during his hyponatremia prevalence studies in tuberculosis patients [6].

Moreover, hyponatremia should be noticed in cerebral, endocrine, pulmonary and neoplastic pathologies. Frequency of severe hyponatremia evaluated as 1.1% in inpatients and in that study, tuberculosis was the most common (24%) underlying condition [22]. In our study frequency of severe hyponatremia was reported as 7.7%.

In 1969, Chung has documented, that approximately in 11% patients, hyponatremia was noted having active Tuberculosis, and the primary evident cause was SIADH [23]. A case of Primary tuberculosis reported by Vorherr *et al*. having hyponatremia and antidiuretic agents were found in infected lung tissues [16]. SIADH has been suggested by Bryant *et al*. in patients having pulmonary infections like Primary tuberculosis [24]. Two cases of Primary tuberculosis reported by Schorn *et al*. and found an abnormal inappropriate ADH level as a rationale mechanism of action [25]. A 74-year-old woman reported by Cockcroft *et al*., having miliary tuberculosis and severe hyponatremia due to syndrome of inappropriate ADH secretion (SIADH) [26]. Usalan *et al*. documented a tuberculosis case and lethargy was revealed due to hyponatremia evidently from SIADH [27]. Lastly, Lee documented a case of primarily tuberculosis having refractory hyponatremia due to syndrome of inappropriate ADH secretion (SIADH) [15].

SIADH has been noted in infectious disorders like tuberculosis. Weiss *et al*., in one of the first reports, documented hyponatremia in patients with primary tuberculosis as a result of SIADH [28]. It was then acknowledged that hyponatremia along with increase in level of antidiuretic hormone in tuberculosis is a strong indicator for ectopic antidiuretic hormone production. Couple of studies illustrated that antidiuretic hormone level was unnoticeable following complete antitubercular therapy. Reports of SIADH linked with pulmonary, CNS-related and miliary tuberculosis are noted. At first presentation more than 60% patients may display with SIADH or hyponatremia in tubercular meningitis. A number of infectious diseases are related with SIADH [29].

Nakashita *et al*. documented a SIADH case induced in a patient of tuberculosis by ethionamide use and proposed that drugs of TB to be taken into consideration as likely reason of SIADH but study conclusion showed that incidence of hyponatremia in those patients who have taken maximum doses of ethionamide was no higher than who taken lesser doses [30].

The other mechanism, as involvement of endocrine system by tuberculosis can prompt hyponatremia and is important to be taken into account in patients with primary tuberculosis. Tuberculosis was shown to involve the suprarenal glands (adrenal glands) directly and this association led to subclinical or overt hyponatremia and adrenal insufficiency. Tuberculosis bacilli may also involve the pituitary gland as in childhood years after tubercular

meningitis treatment in 20% of the cases hypopituitarism has been reported. The appeared reason was tubercular lesions impressing the pituitary stalk, hypophysis cerebri (hypothalamus), and directly or indirectly, itself the hypophysis (pituitary gland) [31].

Hyponatremia induced by primary tuberculosis is usually mild to moderate, self-limited and asymptomatic. Most of SIADH cases are reversible with effective primary tuberculosis therapy. Without enough attention by physician SIADH could be overlooked. Conversely TB patients of hyponatremia were more likely at risk of increased mortality.

Moreover, occurrence of hyponatremia in AIDS patients with tuberculosis is higher. Smith *et al*. showed that hyponatremia was found in 60% patients of AIDS diagnosed with generalized tuberculosis; however half of these patients of disseminated tuberculosis after death were only diagnosed. The positive HIV patients were overruled in our study, and can be the logic of the variations between others and our findings [6].

Hypokalemia was noted among the patients of tuberculosis in our study of electrolyte imbalances and no enough research was found on hypokalemia during tuberculosis. 31.3% hyponatremia was noted by Sonya Shin MD during her research on tuberculosis patients taking treatment for MDR-TB (Multi-Drug Resistant Tuberculosis) [32]. MDR-TB patients medicated with injectable agents or tablets and the commonly negative reaction found is hypokalemia. Amikacin, Rifampicin, and Viomycin-pyrazinamide are considered to be linked with electrolytes imbalance, comprising hypokalemia [33].

Baskaran documented that Hypomagnesemia contributing to hypokalemia and hypocalcemia, taking place in patients with PTB as a major abnormality and getting worse by streptomycin use [34]. Capreomycin and Amikacin are aminoglycoside antibiotics [3]. It has been documented that the use of amikacin and capreomycin results in increase renal wasting of electrolyte including magnesium, potassium and calcium [33]. Electrolyte imbalances especially hypokalemia is linked with several notable morbidities such as seizures, tetany, and cardiac arrhythmia [35]. Because of this, potassium level in serum is one of the most notable parameters regarding the safety of patients [33] (Figure 1-7).

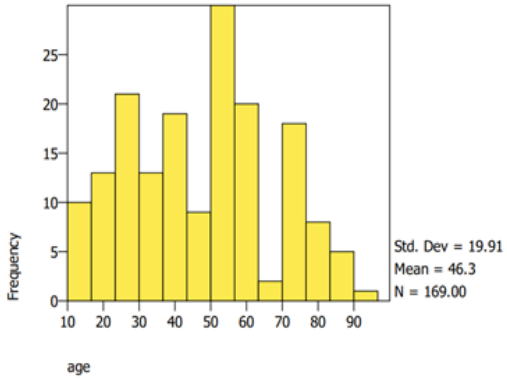

Figure 1 Age histogram

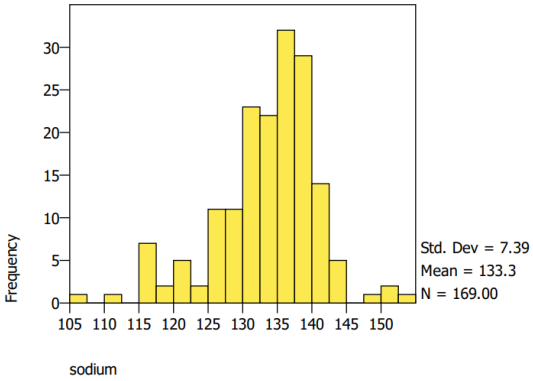

Figure 2 Sodium histogram

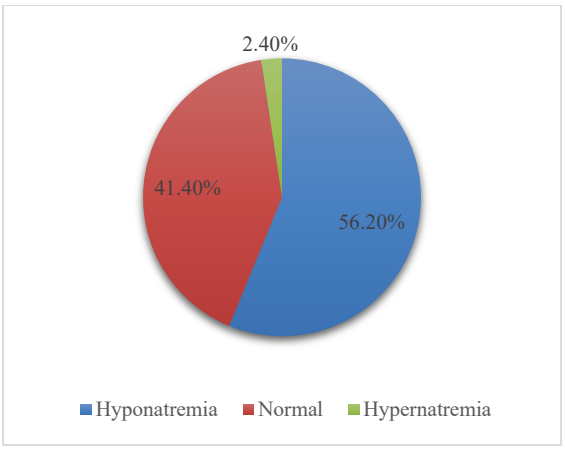

Figure 3 Pie chart showing frequency of different sodium levels

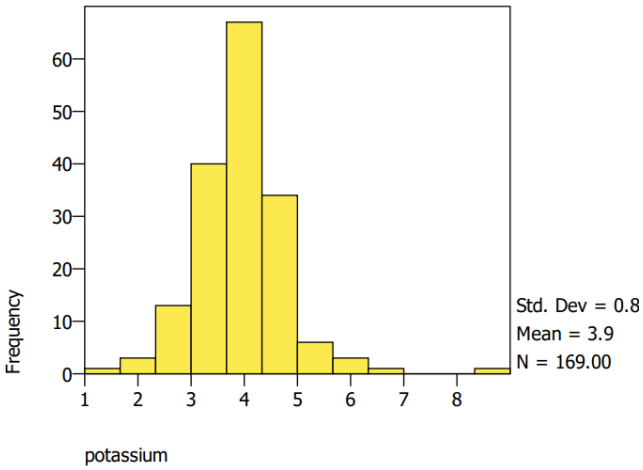

Figure 4 Potassium histogram

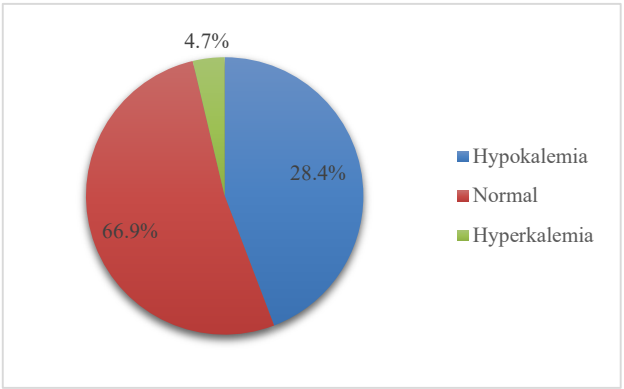

Figure 5 Pie chart showing frequency of different potassium levels

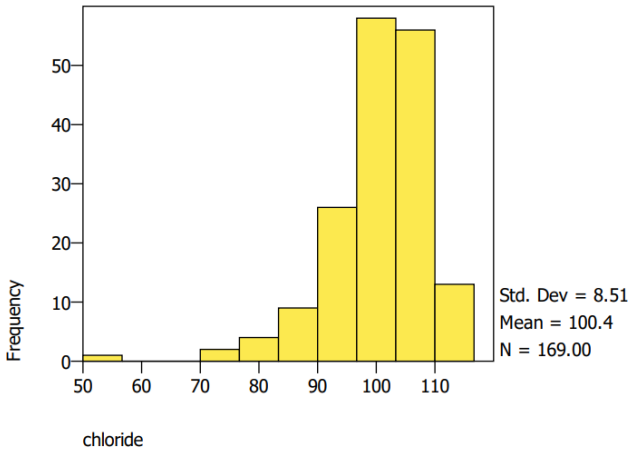

Figure 6 Chloride histogram

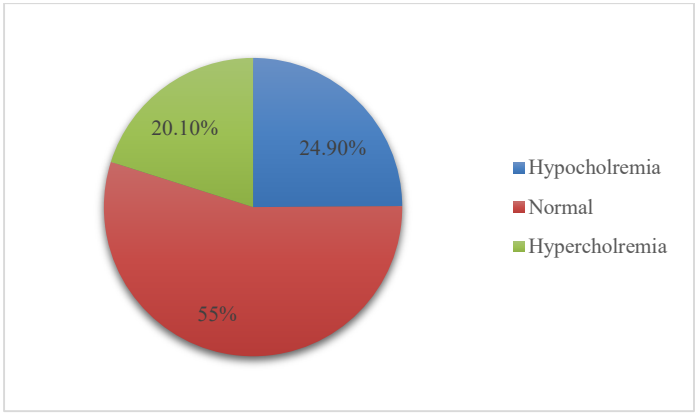

Figure 7 Pie chart showing frequency of different chloride levels

CONCLUSION

Study is conducted on tuberculosis patients admitted to a teaching hospital and deals with serum electrolytes profile analysis. Study shows prevalence of hyponatremia (56.2%) and hypokalemia (28.4%) in tuberculosis patients receiving antitubercular therapy. Additionally, study also record hypochloremia (24.9%) and hyperchloremia (21.1%) in tuberculosis patients receiving antitubercular therapy.

ACKNOWLEDGMENT

The authors admire all the participants.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

All expenses financed by authors themselves.

Ethical Review

After getting ethical clearance the research was performed.

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