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Case Series

Biochemistry Section

Pseudohyponatraemia and Pseudohypokalaemia Due to Lipaemic Samples: A Series of Seven Cases

SWATI DIGAMBAR SAWANT[1], KAMALAKAR MANE[2], TAMILVENDHAN ARUMUGAM[3], ATUL PATIL[4]

ABSTRACT

Pseudohyponatraemia and pseudohypokalaemia are laboratory artifacts caused by analytical interference rather than true electrolyte deficiency. Lipaemia, most commonly due to hypertriglyceridaemia, can result in falsely low sodium and potassium values when measured using indirect Ion-Selective Electrode (ISE) methods, leading to potential misinterpretation and inappropriate clinical management. This case series included seven patients whose lipaemic serum samples showed spuriously low sodium and potassium levels on indirect ISE analysers. Clinical history, biochemical findings, and triglyceride concentrations were reviewed. Electrolyte measurements were repeated using direct ISE methodology and/or after ultracentrifugation to confirm analytical interference. All seven cases demonstrated falsely low sodium and potassium values when analysed using indirect ISE, while repeat testing by direct ISE showed values within the reference range. None of the patients exhibited clinical symptoms consistent with hyponatraemia or hypokalaemia. Increasing severity of lipaemia was associated with greater underestimation of electrolyte concentrations. A notable finding in the present series was the consistent discrepancy between indirect and direct ISE measurements across all patients, highlighting the significant impact of lipaemia on electrolyte estimation. This observation emphasises the importance of correlating laboratory results with clinical findings and confirming abnormal values before initiating treatment. Lipaemia is a significant cause of pseudohyponatraemia and pseudohypokalaemia in routine biochemical analysis. Awareness of this interference is essential to prevent diagnostic errors and unnecessary treatment. Confirmation using direct ISE or ultracentrifugation should be performed before reporting abnormal electrolyte values in lipemic samples.

Keywords: Electrolyte interference, Hypertriglyceridaemia, Ion selective electrode, Laboratory artifact, Lipaemia

INTRODUCTION

Electrolyte disturbances such as hyponatremia and hypokalemia are among the most commonly encountered biochemical abnormalities in clinical practice. They can indicate serious underlying pathologies and often require prompt investigation and management. However, in certain situations, laboratory artifacts may produce falsely low electrolyte values, a condition known as pseudohyponatraemia or pseudohypokalaemia [1].

Pseudohyponatraemia is a laboratory phenomenon wherein serum sodium appears falsely decreased despite normal plasma osmolality and true sodium concentration. This occurs when the aqueous phase of plasma is reduced due to a significant increase in non-aqueous components such as lipids or proteins [2]. Lipaemia, defined as the presence of a high concentration of lipids (particularly triglycerides) in the serum, is a well-known source of pre-analytical and analytical interference [3]. Pseudohypokalaemia, though less commonly discussed, can also result from lipemic interference or cellular uptake of potassium in vitro, particularly in leucocytosis or thrombocytosis [4]. This case series presents seven patients with apparent hyponatremia or hypokalemia due to lipemic interference in laboratory samples.

CASE SERIES

Case 1

A 56-year-old male with a 5-year history of type 2 diabetes mellitus and dyslipidaemia presented for routine biochemical evaluation. He was clinically stable and asymptomatic, with no history of muscle weakness, paresthesia, palpitations, or gastrointestinal symptoms suggestive of electrolyte imbalance. Initial electrolyte analysis performed using an indirect ISE method revealed hyponatremia (sodium 129 mmol/L) and hypokalemia (potassium 2.8 mmol/L). Serum appeared visibly lipemic, and triglyceride concentration was markedly elevated at 950 mg/dL [Table/Fig-1]. In view of the absence of clinical features of hypokalemia and significant lipaemia, repeat electrolyte testing was performed on the same day (within a few hours) using a direct ISE method, which showed a normal potassium level of 4.2 mmol/L and sodium level of 137 mmol/L [Table/Fig-2]. Electrocardiography did not show any abnormalities suggestive of hypokalemia. The findings were consistent with lipaemia-induced pseudohyponatraemia and pseudohypokalaemia; therefore, potassium supplementation was not initiated .The patient was advised management for hypertriglyceridaemia with follow-up monitoring.

Case	Age (years)	Sex	Underlying condition	Clinical symptoms of electrolyte imbalance	Lipaemia noted
1	56	M	Diabetes mellitus, Dyslipidaemia	None	Yes
2	42	F	Hypertriglyceridaemia	None	Yes
3	65	M	Metabolic syndrome	None	Yes
4	38	M	High-fat diet	None	Yes
5	50	F	Alcohol-induced pancreatitis	None	Yes
6	45	M	Obesity	None	Yes
7	29	M	Familial hyperlipidaemia	None	Yes

[Table/Fig-1]: Demographic and clinical characteristics of patients.

Case 2

A 42-year-old woman with a three year history of hypertriglyceridaemia [Table/Fig-1] underwent laboratory evaluation during follow-up. She had no symptoms suggestive of electrolyte disturbance and was haemodynamically stable. Initial electrolyte analysis performed using an indirect ISE method

Case No.	Triglycerides (mg/dL)	Sodium (Indirect ISE) (mmol/L)	Sodium (Direct ISE) (mmol/L)	Potassium (Indirect ISE) (mmol/L)	Potassium (Direct ISE) (mmol/L)
1	950	129	137	2.8	4.2
2	1100	128	138	3.1	4.5
3	870	130	139	2.9	4.1
4	1200	127	136	2.7	4.3
5	980	128	137	3.0	4.4
6	1050	126	135	2.6	4.5
7	900	131	140	3.2	4.0

[Table/Fig-2]: Comparison of electrolyte values obtained by indirect and direct ISE in lipemic samples.
Reference range- Sodium: 135-145 mmol/L; Potassium: 3.5-5.1 mmol/L; Triglycerides: <150 mg/dL; ISE: Ion-Selective Electrode

showed hyponatremia (sodium of 128 mmol/L) and hypokalemia (potassium of 3.1 mmol/L).The serum sample was grossly lipemic, and triglyceride concentration was markedly elevated at 1100 mg/dL. In view of the absence of clinical features suggestive of electrolyte imbalance and the presence of significant lipaemia, repeat electrolyte testing was performed on the same day using a direct ISE analyser. This revealed potassium 4.5 mmol/L and sodium 138mmol/L [Table/Fig-2], confirming that the initial low values were spurious. Electrocardiographic evaluation did not show any abnormalities suggestive of hypokalemia. The patient did not require any therapeutic intervention, and the abnormal results were attributed to lipaemia-related analytical interference. She was advised further management and follow-up for hypertriglyceridaemia.

Case 3

A 65-year-old male with metabolic syndrome, including obesity, hypertension, and dyslipidaemia [Table/Fig-1], was evaluated during routine testing. Indirect ISE measurement showed hypokalemia with a potassium concentration of 2.9 mmol/L and hyponatremia with sodium concentration of 130 mmol/L. Serum triglyceride levels were elevated at 870 mg/dL, and the sample appeared lipemic. The patient had no neuromuscular or cardiac symptoms and no electrocardiographic changes suggestive of hypokalemia. In view of the lipemic sample and absence of clinical features of electrolyte imbalance, repeat electrolyte testing was performed on the same day approximately two hours after the initial analysis using a direct ISE method, which demonstrated sodium 139 mmol/L and potassium 4.1 mmol/L [Table/Fig-2], both within the reference range. The discrepancy between indirect and direct ISE results confirmed pseudohyponatraemia and pseudohypokalaemia secondary to lipaemic intereference, and the patient was advised evaluation and management for underlying dyslipidaemia with follow-up monitoring.

Case 4

A 38-year-old male on a self-reported high-fat diet [Table/Fig-1] presented for routine health screening. Laboratory analysis using indirect ISE revealed hyponatremia (sodium 127mmol/L) and hypokalemia with a potassium level of 2.7 mmol/L. Serum triglyceride concentration was markedly elevated at 1200 mg/dL, and the sample appeared grossly lipemic. The patient was asymptomatic, and physical examination findings were unremarkable. Electrocardiographic evaluation did not show any abnormalities suggestive of hypokalemia. Repeat testing using direct ISE method on the same day showed a potassium concentration of 4.3 mmol/L and sodium concentration of 136 mmol/L [Table/Fig-2], confirming that the initial low value was due to lipemic interference rather than true electrolyte deficiency. The patient was advised evaluation and management for hypertriglyceridaemia with follow-up.

Case 5

A 50-year-old woman with a 2-year history of alcoholic pancreatitis [Table/Fig-1] underwent biochemical evaluation during follow-up. Initial electrolyte analysis performed using an indirect ISE method showed hyponatremia (sodium 128 mmol/L) and hypokalemia with a potassium level of 3.0 mmol/L. Serum triglyceride levels were elevated at 980 mg/dL, and the sample appeared lipemic. The patient did not exhibit any signs or symptoms suggestive of electrolyte imbalance, and electrocardiographic evaluation did not reveal abnormalities indicative of hypokalemia. Considering the lipemic nature of the sample, repeat electrolyte testing was performed on the same day using a direct ISE method, which showed sodium 137 mmol/L and potassium 4.4 mmol/L [Table/Fig-2], both within the reference range. These findings confirmed lipaemia-induced pseudohyponatraemia and pseudohypokalaemia. The patient was advised further evaluation and management of hypertriglyceridaemia with follow-up monitoring.

Case 6

A 45-year-old obese male [Table/Fig-1] with no acute complaints was evaluated as part of routine metabolic assessment. Initial electrolyte analysis performed using an Indirect ISE method showed hyponatremia (sodium 126 mmol/L) and hypokalemia with a potassium concentration of 2.6 mmol/L. Serum triglyceride levels were elevated at 1050 mg/dL and the sample showed visible lipaemia. The patient was clinically asymptomatic, and there was no evidence of cardiac or neuromuscular involvement. In view of significant lipaemia and absence of clinical features of electrolyte imbalance, repeat electrolyte testing was performed within few hours using direct ISE method, which showed sodium 135 mmol/L and potassium level of 4.5 mmol/L [Table/Fig-2]. These findings confirmed spurious hyponatremia and hypokalemia related to lipemic interference, and the patient was advised evaluation and management for underlying hypertriglyceridaemia with follow-up monitoring.

Case 7

A 29-year-old male with familial hyperlipidaemia diagnosed four years earlier [Table/Fig-1] presented for routine laboratory monitoring. Initial indirect ISE analysis showed a sodium level of 131 mmol/L and potassium level of 3.2 mmol/L, with triglyceride levels of 900 mg/dL. Despite the laboratory findings, the patient had no clinical manifestations of hypokalemia and electrocardiographic evaluation did not reveal any abnormalities. Repeat analysis using direct ISE on the same day revealed a normal sodium concentration of 140mmol/L and potassium concentration of 4.0 mmol/L [Table/Fig-2], both within the reference range. These findings were consistent with lipaemia-induced pseudohyponatraemia and pseudohypokalaemia, and the patient was advised evaluation and management for familial hyperlipedemia with follow-up monitoring.

Across all cases, indirect ISE results suggested hyponatremia and hypokalemia, whereas direct ISE measurements were within the reference range.

DISCUSSION

Pseudohyponatraemia and pseudohypokalaemia are important laboratory artifacts that may lead to diagnostic confusion and inappropriate clinical management if not recognised promptly. In the present case series, all seven patients demonstrated falsely low sodium and potassium concentrations when analysed using the indirect ISE method, whereas repeat testing using direct ISE showed values within the reference range. These findings highlight the significant effect of lipaemia on electrolyte estimation when dilution-based analytical methods are used. Similar observations have been reported in previous studies describing pseudohyponatraemia

associated with hyperlipidaemia and methodological limitations of indirect ISE techniques [5,6]. Under normal physiological conditions, plasma consists of approximately 93% water and 7% non-aqueous components such as lipids and proteins. Electrolytes are present only in the aqueous phase of plasma. When the concentration of lipids or proteins increases markedly the proportion of plasma water decreases resulting in falsely low electrolyte concentrations when measured using dilution-dependent techniques such as indirect ISE. This phenomenon is referred to as the electrolyte exclusion effect and represents the principal mechanism underlying pseudohyponatraemia in patients with hypertriglyceridaemia or hyperproteinaemia [2,7].

Lipaemia is one of the most frequently encountered causes of analytical interference in clinical chemistry laboratories. Severe hypertriglyceridaemia can significantly alter the composition of plasma, thereby affecting electrolyte measurements obtained by automated analysers that employ indirect ISE methodology [6,8]. In contrast, direct ISE methods measure electrolyte activity in the plasma water fraction without prior dilution and are therefore largely unaffected by variations in lipid or protein concentrations [2,9]. This explains the normalisation of sodium and potassium values observed in the present study when repeat testing was performed using direct ISE. Although lipaemia was the cause of pseudoelectrolyte abnormalities in our cases, other conditions must also be considered in the differential diagnosis of spurious electrolyte results.

Hyperproteinaemia, particularly in disorders such as multiple myeloma or monoclonal gammopathy, may produce similar analytical interference by increasing the solid fraction of plasma and reducing the aqueous phase available for electrolyte distribution [10,11]. Several studies have demonstrated discrepancies between direct and indirect ISE measurements in patients with abnormal plasma protein concentrations, emphasising the importance of recognising hyperproteinaemia as an alternative cause of pseudohyponatraemia [12-14]. In addition to pseudohyponatraemia, pseudohypokalaemia may occur due to several preanalytical factors. One commonly reported mechanism is prolonged storage of blood samples at room temperature before analysis. During this period, metabolically active blood cells, including erythrocytes and leukocytes, may continue to uptake potassium from the extracellular fluid, leading to falsely reduced serum potassium concentrations. This effect is particularly evident when there is a delay in sample processing or in conditions associated with increased cellular activity, such as leukocytosis [4,13]. Proper handling and timely analysis of specimens are therefore essential to minimise such errors.

Another factor contributing to analytical variability is the methodological difference between electrolyte measurement techniques. Studies comparing direct and indirect ISE methods have reported significant differences in sodium estimation in critically ill patients and in samples with altered plasma composition [8,14]. These discrepancies may have clinical implications, particularly when treatment decisions are based solely on laboratory values. Therefore, confirmatory testing using direct ISE or alternative methods should be considered when laboratory results are inconsistent with clinical findings. Correlation of laboratory data with clinical presentation remains a critical step in identifying pseudoelectrolyte disorders. In the present case series, none of the patients exhibited clinical features suggestive of hyponatremia or hypokalemia, and electrocardiographic findings were normal. Such discordance between laboratory results and clinical status should prompt further investigation for possible analytical interference. Previous reports have similarly emphasised that pseudohyponatraemia should be suspected when electrolyte abnormalities are not supported by clinical evidence [6].

From a laboratory quality management perspective, recognition of analytical interference is an essential component of good laboratory practice. International standards and guidelines, including those from the Clinical and Laboratory Standards Institute (CLSI) and the International Organisation for Standardisation (ISO 15189), emphasise the importance of identifying pre-analytical and analytical sources of error in clinical laboratory testing [15,16]. Recommended practices include visual inspection of serum samples for lipaemia, verification of unexpected laboratory results, and repeat testing using alternative analytical techniques when interference is suspected. In routine laboratory practice, additional measures such as measurement of serum triglyceride levels, ultracentrifugation of lipemic samples, or analysis using direct ISE can help confirm suspected cases of pseudohyponatraemia and pseudohypokalaemia. Implementation of such protocols improves diagnostic accuracy and prevents unnecessary therapeutic interventions [17,18]. The findings of this study reinforce the importance of awareness among both clinicians and laboratory professionals regarding lipaemia-related analytical interference. Early recognition of pseudoelectrolyte abnormalities helps avoid inappropriate treatment, reduces healthcare costs, and improves patient safety. Furthermore, close communication between clinicians and laboratory personnel plays a crucial role in ensuring accurate interpretation of laboratory results.

CONCLUSION(S)

This case series highlights lipaemia as an important cause of pseudohyponatraemia and pseudohypokalaemia associated with indirect ISE analysis. Awareness of this analytical interference is essential to prevent misinterpretation of laboratory results and unnecessary treatment. Confirmation of electrolyte abnormalities using direct ISE or ultracentrifugation should be considered mandatory in lipemic samples before clinical intervention.

Ethical Approval and Patient Consent: This study was conducted as a case series involving seven patients with lipemic interference in electrolyte analysis. The study protocol was reviewed and approved by the Institutional Ethics Committee (Approval No.: Biochemistry/249/25).

Written informed consent for publication of clinical details and laboratory findings was obtained from all seven patients included in this study.

All procedures performed were in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. Patient identities have been anonymised to ensure confidentiality.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, Dr. Vaishampayan Memorial Government Medical College, Solapur, Maharashtra, India.
2. Professor and Head, Department of Biochemistry, Dr. Vaishampayan Memorial Government Medical College, Solapur, Maharashtra, India.
3. Junior Resident III, Department of Biochemistry, Dr. Vaishampayan Memorial Government Medical College, Solapur, Maharashtra, India.
4. Assistant Professor, Department of Biochemistry, Government Medical College, Sindhudurg, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Tamilvendhan Arumugam,
Junior Resident III, Department of Biochemistry, Dr. Vaishampayan Memorial Government Medical College, Solapur-413003, Maharashtra, India.
E-mail: dr.tamilvendhan20@gmail.com

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