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ASSESSMENT OF ELECTROLYTE IMBALANCE, INCLUDING HYPOKALEMIA, IN TYPE 2 DIABETES MELLITUS PATIENTS: A COMPARATIVE STUDY OF LONG-TERM INSULIN THERAPY VERSUS ORAL HYPOGLYCEMIC MEDICATIONS

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ABSTRACT

Background: Electrolyte imbalances are commonly observed in diabetes mellitus (DM) and can lead to significant complications. Understanding the underlying mechanisms of these disturbances may facilitate pathophysiology-directed therapy, potentially preventing the adverse effects associated with electrolyte disorders and their management. Diabetes mellitus is a global health challenge and one of the most rapidly increasing metabolic diseases. Among the electrolyte abnormalities, hypokalemia is frequently seen in type 2 diabetes mellitus (T2DM) patients, particularly those receiving exogenous insulin therapy. Objective: This study aims to assess electrolyte imbalances, specifically hypokalemia, in T2DM patients and compare the effects of long-term insulin therapy combined with oral hypoglycemic agents (OHAs) versus treatment with OHAs alone. Methods: This observational, comparative, cross-sectional study was conducted at the Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India, between January 2021 to June 2021. A total of 100 T2DM patients aged 40–80 years were enrolled and divided into two groups: Group 1 (n = 50): Patients on both insulin and OHAs. Group 2 (n = 50): Patients on OHAs alone. Electrolyte levels, particularly serum potassium, were analyzed and compared between the two groups. Results: The majority of participants were aged between 51 and 60 years, with a slight predominance of female patients. A significant presence of electrolyte disturbances was observed, with hypokalemia being more pronounced in patients receiving insulin therapy. Uncontrolled blood sugar levels were associated with an increased incidence of electrolyte imbalance. Conclusion: Electrolyte imbalance, particularly hypokalemia, is prevalent in T2DM patients, especially those on insulin therapy. Routine monitoring of serum electrolytes is essential for preventing complications and improving patient outcomes. Exogenous insulin use should be carefully regulated, with adherence to appropriate indications, optimal dosing, and frequent potassium level assessments to enhance the quality of life in T2DM patients.

Key words: Electrolyte Imbalance, Hypokalemia, Type 2 Diabetes Mellitus, Insulin.

INTRODUCTION

Electrolyte imbalances are frequently encountered in clinical practice, particularly among hospitalized patients, ranging from asymptomatic individuals to critically ill cases. These disturbances are associated with increased morbidity and mortality, making them a significant concern in both hospital and community settings. Even mild or chronic community-acquired electrolyte imbalances have been linked to poor health outcomes [1]. Electrolyte disorders are typically multifactorial, influenced by factors such as nutritional deficiencies, gastrointestinal absorption issues, acid-base imbalances, pharmacological agents, comorbidities

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(particularly renal disease), and acute illnesses [2,3].

Diabetes mellitus (DM) is a widespread and growing global health concern, recognized as the fastest-increasing metabolic disorder. It ranks as the third most prevalent disease worldwide, affecting 7.1% of the Indian population and approximately 1.5% of the global population [4]. The hallmark of DM is persistent hyperglycemia, either due to insufficient insulin production or impaired insulin function [1,5]. The ancient physician Sushruta first described diabetes as a condition characterized by excessive excretion of sweet-tasting urine. The discovery of insulin-producing islet cells in the pancreas was made by German medical student Paul Langerhans in 1869 [6].

A similar diabetic state was observed in dogs that underwent pancreatectomy, leading to early attempts to treat diabetes using pancreatic extracts. In the early 20th century, Berlin-based physician Georg Zuelzer attempted to treat a diabetic patient using pancreatic extract. Further research between 1916 and 1920 by Romanian physiologist Nicolas Paulesco demonstrated that injecting pancreatic extracts into diabetic dogs reduced their urinary sugar and ketone levels [7]. The breakthrough discovery of insulin came in 1921 when Frederick Banting and Charles Best successfully extracted an active pancreatic substance that lowered blood glucose levels in diabetic dogs. Their refined insulin extract was first administered to 14-year-old Leonard Thompson, whose blood glucose level was initially 500 mg/dL [8]. This success led to large-scale insulin production using extracts from pigs and cows, and later, recombinant DNA technology facilitated the development of human insulin for therapeutic use [9].

Both type 1 and type 2 diabetes mellitus patients often require exogenous insulin therapy. Insulin exerts its effects by stimulating the GLUT4 transporter, facilitating glucose uptake into cells. Additionally, insulin promotes potassium influx into skeletal muscle and hepatic cells by enhancing Na^+/K^+ ATPase activity [10].

Potassium, the primary intracellular cation, is predominantly stored within cells (98%), with 70% found in muscles, 20% in vital organs including the brain, and 10% in the skin and subcutaneous tissues. Normal serum potassium levels range between 3.5 and 5.0 mmol/L [11]. Hypokalemia, defined as a serum potassium level below 3.5 mmol/L, can result from inadequate dietary intake, gastrointestinal losses, renal excretion, or medication use. Certain drugs, including exogenous insulin, salbutamol, theophylline, diuretics, laxatives, and amphotericin B, contribute to potassium depletion [12,13].

Hypokalemia is particularly concerning in diabetic patients as it impairs insulin secretion and reduces peripheral glucose utilization, resulting in poor glycemic control and worsening hyperglycemia. This creates a vicious cycle where hypokalemia exacerbates diabetes management challenges and vice versa [14]. Insulin therapy lowers serum potassium by driving it into cells, and prolonged insulin use can lead to significant potassium depletion. Severe hypokalemia is associated with complications such as cardiac conduction abnormalities, muscle weakness, fatigue, cramps, paralytic ileus, and carbohydrate intolerance [15].

This study aims to compare the prevalence of hypokalemia and other electrolyte imbalances in type 2 diabetes mellitus patients treated with a combination of insulin and oral hypoglycemic agents (OHAs) versus those on OHAs alone. By monitoring the impact of exogenous insulin therapy on electrolyte homeostasis, particularly potassium levels, this study seeks to assess potential insulin-related adverse effects and improve the clinical management of T2DM patients.

MATERIAL AND METHODS

A total of 100 patients were included in this investigation. This study was conducted at the Department of Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India. The study was conducted from January 2021 to June 2021. This study is an observational, comparative, cross-sectional study comparing Type 2 Diabetes Mellitus patients on long-term insulin therapy and oral hypoglycemic medications with patients solely on oral hypoglycemic agents.

InclusionCriteria:

- Individuals between the ages of 40 and 80;
- Both men and women;
- Tose who are open to taking part in the study.

ExclusionCriteria:

- Patients with renal impairment;
- Patients with Type 1 Diabetes Mellitus on Insuline;
- Patients unwilling to participate and provide consent

Studyprocedure

Patients will receive detailed explanations regarding the study's objectives and protocols. Patients who wish to participate in the study will be required to provide informed consent in the specified manner in the local language. We will collect the demographic information of the patients. Patients who meet the specified criteria will be included in the trial.

RESULTS

This study aimed to evaluate electrolyte imbalance, particularly hypokalemia, resulting from exogenous insulin therapy and the adverse effects of insulin in patients with type 2 diabetes mellitus who are taking both insulin and oral hypoglycemic agents, compared to patients with type 2 diabetes mellitus who are only taking oral hypoglycemic agents.

Table 1: Patients with insulin and OHA

Totalnoofpatients	Patients receiving insulin and OHA	Patients receiving only OHA
100	50	50

Table 1 displays the total number of patients receiving insulin (50) and oral hypoglycemic agents (OHA), as well as individuals receiving only OHA (50).

Table 2:Agewise Distribution

Sr. No.	Age(Yrs.)	Patients	%
1.	40-50	25	25%
2.	51-60	35	35%
3.	61-70	30	30%
4.	71-80	20	20%

Table 2 displays the age distribution of the patients. The age group 51-60 had a higher number of patients compared to the 40-50 age group.

Table 3: Gender wiseDistribution

Sr. No.	Gender	Patients	%
1.	Male	46	46%
2.	Female	54	54%
3.	Total	100	100%

Table 3 displays the gender distribution of the patients. There were 54% females and 46% males.

Table 4: Patients with hypokalemia and Normokalemia

Sr. No.		Hypokalemia	Normokalemia
1.	Patientsoninsulin And OHA	50%	60%
2.	Patients on only OHA	50%	40%

Table 4 displays the percentage of patients with hypokalemia among those on insulin and OHA compared to those solely using OHA. Diabetic patients who take both insulin and oral hypoglycemic agents have a higher incidence of hypokalemia.

Table 5: Insulin and oral hydroxyantacid-treated individuals' serum potassium levels

	Patients on Insul in and OHA		
	Normalrange	Study grouprange	Mean
SerumPotassium	3.4-5.1	2.5-5.2	3.084±0.358

Table 5 displays the average potassium levels in patients who are using insulin and oral hypoglycemic agents (OHA). 100 patients who were receiving insulin and oral hypoglycemic agents were studied.

Table 6: Blood potassium levels in individuals solely using OHA

	Patientson OHA		
	Normalrange	Study grouprange	Mean
SerumPotassium	3.5.5-5.3	3.3-5.3	4.0±0.562

Table 6 displays the average potassium levels in patients on oral hypoglycemic agents (OHA). 100 patients who were receiving oral hypoglycemic agents (OHA) were studied

DISCUSSION

Electrolyte imbalance is commonly present in patients with type 2 diabetes mellitus. The cause is usually multifactorial, but usually results from insulin deficiency in diabetic ketoacidosis and hyperglycemia. Electrolytes play an important role in several body mechanisms, to name a few it helps maintain acid base balance, membrane potential, muscle contraction, nerve conduction and control body fluid. Alterations in electrolytes homeostasis may lead to physiologic disorders. Insulin has been shown to activate Na± /K± -ATPase enzyme. Therefore, low serum insulin level reduces Na± /K± -ATPase activity with poor Na± and K ± metabolism as a result and so transport across biomembranes as well as hindered monosaccharide uptake by intestinal epithelia occurs. In diabetes mellitus, hyperglycemia causes glucose induced osmotic diuresis with resultant loss of body fluids and electrolytes.

When treating diabetes mellitus type 1, type 2, hyperkalemia, and gestational diabetes mellitus, exogenous insulin is among the most popular drugs used. Insulin regulates the metabolic processes of numerous tissues, affects cell proliferation, and encourages glucose and adipose storage within specialised target cells. Treatment of diabetic ketoacidosis and hyperglycemic hyperosmolar

coma also involves the administration of insulin. Insulin comes in a variety of modalities for administration, including subcutaneous injection, inhaled insulin, and continuous subcutaneous infusion devices. Some of the side effects of using exogenous insulin include hypoglycemia, lipodystrophy, allergies, and edoema. Serious consequences such as paralytic ileus, arrhythmias, and muscle cramps can develop from hypokalemia, which is prevalent in people using exogenous insulin for an extended period of time [13-15].

This study examined the effects of insulin and oral hypokalemia on electrolyte imbalances in patients with type 2 diabetes mellitus. One hundred patients were split evenly between the two groups. In one group, 50 patients with type 2 diabetes mellitus who were using insulin in addition to OHA were included, and in the other group, 50 patients who were taking OHA alone were included. Participants' ages vary from forty to eighty. According to the age distribution, there are more patients between the ages of 51 and 60, and when looking at the sex distribution, there are somewhat more female patients than male patients [16-18].

In a study involving 100 individuals with type 2 diabetes mellitus, serum electrolytes were taken. Among those patients, 63% had hypokalemia while taking insulin and OHA together, while 12% had it while taking OHA alone for over 5 years. When people use insulin for an extended period of time, their serum potassium levels drop significantly [19, 20]. The average serum potassium level in individuals receiving both exogenous insulin and oral hydroxyacetone is 3.083mMol/L, while the average serum potassium level in patients receiving OHA alone is 3.997mMol/L. There is a statistically significant difference between patients taking insulin and OHA and those taking OHA alone. In individuals receiving insulin and OHA, 36 experience mild hypokalemia, 25 moderate hypokalemia, and 2 severe cases; in those taking only OHA, 12 cases of mild hypokalemia occur [20-22].

When administered exogenously, insulin increases the activity of the Na+-K+-ATPase pump, which in turn promotes the entrance of K+ into hepatic cells and skeletal muscles, leading to hypokalemia. Hypoglycemia caused by insulin may also contribute by increasing adrenaline secretion. When treating extreme hyperglycemia, insulin injection is the most common cause of hypokalemia. Potassium deficiency is a common complication of diabetic ketoacidosis and HHS. Hyperglycemia and carbohydrate intolerance result from impaired insulin production and reduced peripheral glucose utilisation, which is caused by hypokalemia. Hypokalemia causes poorly controlled diabetes mellitus, which in turn causes hypokalemia, creating a vicious cycle in diabetic individuals [23-25].

Among the type 2 diabetes mellitus patients enrolled in this trial, 63% had hypokalemia while taking insulin and OHA together, while 12% shown hypokalemia while taking OHA alone. This lends credence to the idea that long-term use of exogenous insulin therapy, which is associated with a host of side effects including weakness, constipation, exhaustion, and muscle cramps, can induce severe hypokalemia in patients with type 2 diabetes mellitus. Due to long-term insulin treatment, most people with type 2 diabetes mellitus experience myalgia, muscular cramps, and exhaustion [26-28].

To avoid hypokalemia, it is vital to utilise insulin appropriately and deliver the optimum doses during long-term therapy while testing serum potassium often. Patients with type 2 diabetes mellitus who use insulin and oral hydroxyanisole have mean serum sodium levels of 135.67 and 136.15, respectively; however, these changes are not statistically significant. Patients with type 2 diabetes mellitus who are taking insulin and oral hydroxyantrol have mean random blood sugar levels of 134.47, while those who are on OHA alone had levels of 143.81. The difference between the two groups is statistically significant [27-29].

Electrolyte abnormalities are common in diabetic patients and may be associated with increased morbidity and mortality. These disturbances are particularly common in decompensated DM, in the elderly as well as in the presence of renal impairment. Patients with DM may receive complex drug regimens some of which may be associated with electrolyte disorders. Discontinuation of these medications, when possible, as well as strict control of glycemia are of paramount importance to prevent electrolyte abnormalities in diabetic patients. The successful management of these disorders can best be accomplished by elucidating the underlying pathophysiologic mechanisms.

Everyone who takes part in this study is asked to fill out a questionnaire about the side effects of insulin. Almost every single patient out of one hundred experienced some sort of unpleasant impact. Fatigue was the adverse impact experienced by the majority of patients. Leg cramps are the second most common sign. Many patients also had palpitations, tremors, and profuse perspiration [30, 31]. The majority of the adverse drug reactions fell into the "possible" or "probable" categories according to the World Health Organization's causation assessment scale. The majority of side effects are classified as mild on the modified Hartwig Siegel scale. Patients will experience a decline in quality of life due to the aforementioned negative effects, which include lethargy, palpitations, muscle cramps, and weariness. Patients on long-term exogenous insulin therapy are at increased risk for these complications. To prevent hypokalemia and its consequences and to improve the quality of life for patients, it is vital to administer exogenous insulin cautiously and at the proper doses while also monitoring serum potassium often [32-33]. Diabetic people should be screened for electrolyte imbalances and steps must be taken to prevent their consequences. Therefore measuring

serum electrolytes in type 2 diabetes patients should be done as part of routine patient care.

CONCLUSION

Electrolytes play an important role in controlling the fluid levels, acid base balance, regulation of neurological and myocardial functions, oxygen delivery and many other biological processes. Patients with Diabetes mellitus are more prone to develop electrolyte imbalances probably due to the complications they develop and the medications they receive. Hence, Screening for electrolyte imbalances should be considered in diabetic population and necessary steps may be taken to prevent its consequences.

Administering exogenous insulin to patients with type 2 diabetes mellitus leads to hypokalemia by facilitating the influx of potassium into skeletal muscles and hepatic cells. This can result from prolonged usage of external insulin. Exogenous insulin should be used judiciously with clear reasons, precise dosing, and regular monitoring of serum potassium levels to prevent problems and enhance quality of life.

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