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

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ABSTRACT
The electrolyte disturbances occurring in DM and describes possible underlying mechanisms . This insight should pave the way for pathophysiology-directed therapy, possibly contributing to the avoidance of several deleterious effects associated with electrolyte disorders and their treatment. Diabetes mellitus is a serious disorder that is widespread globally. It is a significant health issue and one of the fastest-growing metabolic diseases. The aim of this study was to examine electrolyte imbalance, namely Hypokalemia caused by exogenous Insulin in individuals with Type 2 Diabetes Mellitus. A total of 100 patients were included in this investigation. This study was conducted at the Department of General Medicine, Sri Venkateswaraa Medical College Hospital and Research, Pondicherry. India. The study was conducted from July 2020 to December 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. This study analysed electrolyte imbalance, namely hypokalemia, in individuals with type 2 diabetes mellitus who were treated with insulin and oral hypoglycemic agents. 100 patients were placed into two groups for the trial. One group consisted of 50 patients with type 2 diabetes mellitus who were taking insulin plus oral hypoglycemic agents, whereas the other group included 50 patients with type 2 diabetes mellitus who were only taking oral hypoglycemic agents. The age bracket mentioned spans from 40 to 80 years. There were more patients aged 51-60 years in the age distribution, while female patients slightly outnumbered male patients in the sex distribution. Electrolyte imbalance is markedly present in patients with uncontrolled blood sugars therefore serum electrolytes should be routinely measured in patients with type 2 diabetes mellitus. In order to prevent problems and improve quality of life, the use of exogenous insulin should be restricted to acceptable indications, doses, and frequent monitoring of serum potassium.

KEY WORDS: Electrolyte Imbalance, Hypokalemia, Type 2 Diabetes Mellitus, Insulin.

INTRODUCTION
Electrolyte imbalances are commonly observed in clinical settings. These disorders are frequently encountered in hospitalized patients, ranging from asymptomatic individuals to those in critical

conditions, and are associated with increased morbidity and mortality [1-3]. Disturbances in electrolyte balance are also commonly seen in individuals outside of hospital settings. Even mild or chronic community-acquired electrolyte disorders can have a negative impact on health outcomes [3]. Electrolyte disturbances are typically multifactorial. Several pathophysiological factors, such as nutritional deficiencies, gastrointestinal absorption issues, coexisting acid-base imbalances, medications, comorbidities (especially renal diseases), or acute illnesses, whether individually or in combination, contribute significantly. Diabetes mellitus is a prevalent global health issue, posing substantial health risks. It is the fastest-growing metabolic disorder and a major health concern. Ranked as the third most common global disease, it affects 7.1% of India's population and 1.5% of the worldwide population. A hallmark of diabetes mellitus is persistent hyperglycemia, which remains despite the body's insulin production or its effectiveness [1, 2]. Sushruta first described diabetes as a condition resulting in an excessive production of sweet-tasting urine. The acinar cells release digestive enzymes, while the islet cells secrete hormones. This discovery was made in 1869 by Paul Langerhans, a German medical student [3, 4]. A comparable condition to diabetes mellitus in humans has been observed in pancreatectomy dogs. In the early 20th century, a Berlin-based physician named GurgZeuler tried using pancreatic extracts to treat a diabetic patient who was on the verge of death. From 1916 to 1920, the physiologist Nicolas Paulesco in Rome found that diabetic dogs injected with pancreatic extracts had reduced urine sugar and ketone levels. Banting and Best in 1921 isolated an active pancreatic extract that lowered blood glucose in diabetic dogs. This extract was initially administered to 14-year-old Leonard Thompson, whose blood sugar level was 500 mg/dL. Following the development of a stable extract by Macleod and J.B. Collip, insulin derived from pigs and cows was used in North America. Human insulin is now produced for therapy through recombinant DNA technology [5-7]. The majority of individuals with type 1 and type 2 diabetes mellitus are managed with exogenous insulin. To facilitate its action, insulin stimulates the GLUT4 transporter, allowing glucose to enter cells. Insulin also promotes the activity of Na+K+ ATPase, helping potassium enter skeletal muscle and liver cells [8-10]. Potassium, an essential cation for cellular function, is predominantly found within cells (98%). It is distributed as 20% in the brain and large organs, 10% in the skin and subcutaneous tissue, and 70% in muscles. A normal serum potassium level ranges from 3.5 to 5 mMol/L. Hypokalemia is defined by a potassium level below 3.5 mMol/L. Causes of hypokalemia include insufficient intake, gastrointestinal or renal losses, and medications like insulin, salbutamol, theophylline, diuretics, laxatives, amphotericin B, and others [9-11]. Hypokalemia is linked to impaired insulin secretion and reduced peripheral glucose uptake, resulting in carbohydrate intolerance and hyperglycemia. This creates a cycle in diabetic patients, where low serum potassium levels worsen diabetes control. By transporting potassium into cells, insulin therapy lowers potassium concentrations. Hypokalemia can thus be a severe adverse effect of insulin administration. The consequences of hypokalemia include cardiac conduction abnormalities, muscle pain, fatigue, cramps, and paralytic ileus. Additionally, hypokalemia contributes to hyperglycemia and carbohydrate intolerance by inhibiting insulin secretion and limiting peripheral glucose utilization. The aim of this study is to compare the occurrence of hypokalemia and other electrolyte disturbances in type 2 diabetic patients receiving both insulin and oral hypoglycemic agents with those on oral hypoglycemic agents alone. The study will monitor hypokalemia, other electrolyte imbalances, and other side effects associated with exogenous insulin therapy [10-12]. This research aims to explore insulin-related side effects, with particular emphasis on electrolyte disturbances such as hypokalemia, in individuals with type 2 diabetes mellitus.

MATERIAL AND METHODS

A total of 100 participants were recruited for this research, which was conducted at the Department of General Medicine, Aarupadai Veedu Medical College and Hospital, Puducherry, June 2024 to September 2024. The study employed an observational, comparative, cross-sectional design, aiming to compare the outcomes of individuals with Type 2 Diabetes Mellitus who were receiving long-term

insulin therapy combined with oral hypoglycemic agents against those undergoing treatment exclusively with oral hypoglycemic medications.

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

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

Study procedure
Participants will be given comprehensive information about the study's aims and procedures. Those who choose to take part in the study will be asked to give their informed consent in the prescribed format in the local language. We will gather demographic details of the participants. Individuals who fulfill the outlined criteria will be included in the trial.

RESULTS
The objective of this study was to assess electrolyte disturbances, especially hypokalemia, caused by exogenous insulin treatment and the side effects of insulin in individuals with type 2 diabetes mellitus who are using both insulin and oral hypoglycemic agents, in contrast to those with type 2 diabetes mellitus who are solely on oral hypoglycemic medications.

Table 1: Patients with insulin and OHA

Total no of patients	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 wise Distribution

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
Serum Potassium	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		
	Normal range	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 imbalances are frequently observed in individuals with type 2 diabetes mellitus. The causes are often multifactorial but generally result from insulin deficiency in diabetic ketoacidosis and hyperglycemia. Electrolytes play a critical role in several physiological functions, including maintaining acid-base balance, membrane potential, muscle contraction, nerve conduction, and regulating body fluids. Disruptions in electrolyte balance can lead to physiological disturbances. Insulin has been shown to activate the Na+/K+-ATPase enzyme. Therefore, reduced serum insulin levels impair Na+/K+-ATPase activity, leading to poor sodium and potassium metabolism, which affects transport across cell membranes and hampers the absorption of monosaccharides by intestinal cells. In diabetes, hyperglycemia causes glucose-induced osmotic diuresis, resulting in the loss of body fluids and electrolytes. Exogenous insulin is one of the most commonly used medications in the treatment of type 1 and type 2 diabetes, hyperkalemia, and gestational diabetes mellitus. Insulin regulates metabolic processes in various tissues, affects cell proliferation, and promotes glucose and fat storage in specialized target cells. It is also crucial in the treatment of diabetic ketoacidosis and hyperglycemic hyperosmolar coma. Insulin is available in various forms for administration, including subcutaneous injection, inhaled insulin, and continuous subcutaneous infusion devices. Some side effects associated with exogenous insulin use include hypoglycemia, lipodystrophy, allergies, and edema. Severe complications such as paralytic ileus, arrhythmias, and muscle cramps can occur due to hypokalemia, which is commonly seen in individuals using exogenous insulin over long periods [13-15]. This study investigated the impact of insulin and oral hypoglycemic agents on electrolyte imbalances, particularly hypokalemia, in patients with type 2 diabetes mellitus. A total of 100 patients were equally divided into two groups. The first group included 50 patients who were receiving insulin along with oral hypoglycemic agents, while the second group comprised 50 patients who were only on oral hypoglycemic agents. Participants' ages ranged from forty to eighty, with the highest number of patients between the ages of 51 and 60, and slightly more females than males [16-18]. In a study involving 100 individuals with type 2 diabetes, serum electrolytes were measured. Among those

taking both insulin and oral hypoglycemic agents, 63% had hypokalemia, while 12% had hypokalemia when using oral hypoglycemic agents alone for more than five years. Prolonged insulin use significantly reduced serum potassium levels [19, 20]. The average serum potassium level in those receiving both insulin and oral hypoglycemic agents was 3.083 mMol/L, compared to 3.997 mMol/L in the OHA-only group. The difference between the two groups was statistically significant. Among those on insulin and OHA, 36 had mild hypokalemia, 25 had moderate hypokalemia, and 2 had severe hypokalemia; in the OHA-only group, 12 had mild hypokalemia [20-22]. When insulin is administered exogenously, it increases the activity of the Na+/K+-ATPase pump, promoting the entry of potassium into liver and skeletal muscle cells, leading to hypokalemia. Hypoglycemia caused by insulin may further contribute by stimulating adrenaline release. Insulin injections, especially in the treatment of severe hyperglycemia, are a common cause of hypokalemia. Potassium deficiency is a frequent complication of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Impaired insulin production and reduced peripheral glucose utilization caused by hypokalemia lead to hyperglycemia and carbohydrate intolerance. Hypokalemia results in poorly controlled diabetes, which exacerbates hypokalemia, creating a harmful cycle in diabetic patients [23-25].

Among the patients with type 2 diabetes mellitus in this trial, 63% experienced hypokalemia when using insulin and oral hypoglycemic agents, while 12% had hypokalemia when using oral hypoglycemic agents alone. This supports the notion that long-term exogenous insulin therapy, associated with side effects such as weakness, constipation, fatigue, and muscle cramps, can lead to severe hypokalemia in patients with type 2 diabetes mellitus. Most individuals with type 2 diabetes mellitus who are on long-term insulin therapy experience muscle pain, cramps, and fatigue [26-28]. To prevent hypokalemia, it is essential to use insulin appropriately, delivering the correct doses during long-term therapy while monitoring serum potassium levels regularly. Patients with type 2 diabetes mellitus who are using insulin and oral hypoglycemic agents have mean serum sodium levels of 135.67 and 136.15, respectively, but these differences are not statistically significant. The mean random blood sugar levels in patients using insulin and oral hypoglycemic agents were 134.47, while those using only oral hypoglycemic agents had levels of 143.81. The difference between the two groups was statistically significant [27-29]. Electrolyte disturbances are common in diabetic patients and are often linked to higher morbidity and mortality. These imbalances are particularly prevalent in cases of decompensated diabetes, in older individuals, and in those with renal impairment. Diabetic patients may be prescribed complex drug regimens, some of which can cause electrolyte imbalances. Discontinuing these medications when possible and maintaining strict blood sugar control are critical to preventing electrolyte disorders in diabetic patients. Proper management of these imbalances is best achieved by understanding the underlying pathophysiological mechanisms. All participants in this study were asked to complete a questionnaire about the side effects of insulin. Nearly every patient experienced some adverse effects. Fatigue was the most common side effect, followed by leg cramps. Many patients also reported palpitations, tremors, and excessive sweating [30, 31]. The majority of adverse drug reactions were classified as "possible" or "probable" according to the World Health Organization's causality assessment scale. Most of the side effects were mild according to the modified Hartwig Siegel scale. The adverse effects, including fatigue, palpitations, muscle cramps, and weakness, negatively impact the quality of life of patients. Those on long-term exogenous insulin therapy are at an increased risk of these complications. To prevent hypokalemia and its associated consequences, and to improve the quality of life for patients, it is crucial to administer exogenous insulin cautiously, in the appropriate doses, and monitor serum potassium levels regularly [32]. Diabetic patients should be routinely screened for electrolyte imbalances, and steps should be taken to prevent their adverse outcomes. Therefore, measuring serum electrolytes in type 2 diabetes patients should be part of regular patient care.

CONCLUSION

Electrolytes are crucial for regulating fluid balance, maintaining acid-base equilibrium, controlling neurological and cardiac functions, facilitating oxygen delivery, and supporting many other physiological processes. Individuals with diabetes mellitus are more likely to experience electrolyte imbalances, likely due to the complications they face and the medications they take. Therefore, it is important to screen for electrolyte imbalances in the diabetic population and take appropriate measures to prevent potential adverse effects. The administration of exogenous insulin in patients with type 2 diabetes mellitus can lead to hypokalemia by promoting the movement of potassium into skeletal muscles and liver cells. This effect may result from prolonged use of insulin. Exogenous insulin should be prescribed carefully, with clear indications, accurate dosing, and regular monitoring of serum potassium levels to avoid complications and improve the patient's quality of life.

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