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Original Article

Effectiveness of Insulin Therapy Optimization in Type 2 Diabetes Mellitus Patients: A Prospective Observational Study

Sudha Murthy*, Shekhar Yadav, Blessy George, Balakeshwa Ramaiah

Department of Pharmacy Practice, Karnataka College of Pharmacy, Bangalore, Karnataka, INDIA.

ABSTRACT

Background: Type 2 Diabetes Mellitus, is an emerging complex metabolic disorder characterized by insulin resistance, impaired glucose uptake and disrupted hepatic glucose production. This study aimed to elucidate the importance of insulin therapy in optimizing glycemic control among T2DM patients. **Materials and Methods:** This prospective, observational study was performed in a tertiary care hospital, Bengaluru. The patient who was prescribed insulin and those already on insulin therapy were interviewed, based on their socio-demographics, insulin therapy, knowledge, and reason to initiate insulin therapy and data was documented in a standard data collection form. **Results:** The analysis population comprised 106 patients. The findings revealed a preponderance of patients (50-59 years) afflicted with T2DM, with a significant proportion (83.96%) initiating insulin therapy. Less than 40% of patient had a poor understanding of the disorder which co-relates to their non-adherence. 95% of the study population accounts for higher HbA_{1c}, increased fasting sugars and uncontrolled diabetes on OHA's were the major criteria to initiate insulin. Notably, hyperglycemia (89.62%) and diabetic neuropathy (84.90%) emerged as prevalent comorbidities. Difficulty in remembering and pain were reasons for refusal. Patients received comprehensive counselling, to enhance their adaptability and proficiency in managing insulin therapy. **Conclusion:** This study concludes that timely initiation of insulin therapy can minimize complications and patients' adherence towards insulin, understanding, and physical activity will improve the efficacy and outcome of therapy. Proper counselling would help improve the patient's specific problems.

Keywords: Insulin regimen, Types of insulin, Diabetes mellitus, HbA_{1c}, OHA.

Correspondence:
Ms. Sudha Murthy
Department of Pharmacy Practice,
Karnataka College of Pharmacy,
Bangalore, Karnataka, INDIA.
Email: sudhamurthy33@gmail.com

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INTRODUCTION

Optimization of insulin therapy is done in order to enhance efficacy of treatment with benefits for T2DM patients' overall well-being and attaining better glycaemic control. T2DM is a multi-factorial disease that includes diverse disturbances in the regulation of insulin, either to peripheral tissue or pancreatic secretion of insulin involved in carbohydrate metabolism. This is influenced by the interaction of genetics, environment, and lifestyle factors.[1] The prevalence of T2DM is alarming; globally, there has been an increase in its growth rate by 80%. Global Burden of Disease data estimates that T2DM affects 462 million individuals worldwide; it stands as the 9th leading cause of death in the world.[2,3]

Some risk factors associated in T2DM as specific genetic predisposition, environmental influence and metabolic factors will increase the likelihood of developing T2DM. Notably, a family history of diabetes across generations, coupled with obesity and a sedentary lifestyle can significantly contribute to T2DM.[4] Smoking nicotine can disrupt glucose metabolism, reducing the ability of muscles to absorb glucose. This cause would be a precursor for insulin resistance.[5]

A mood disorder has a profound effect on a patient's mental well-being setting a physiological change, which increases the activity in the sympathetic system and hypothalamic-pituitary-adrenal axis, leading to elevated levels of catecholamines and inflammation. Over time, it fuels insulin resistance.[6,7]

The risk of developing T2DM increases steadily with advancing age, many research studies as considered age as a significant independent risk factor for T2DM progression.[8] Several cohort studies across countries have consistently shown that engaging in moderate-intense physical activity can gradually lower disease progression. In contrast, a sedentary lifestyle would decrease insulin sensitivity which can potentially trigger a cascade of

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events causing beta-cell dysfunction and impaired glucose tolerance/ insulin resistance.[9]

Carrying excess weight is the leading contributor to the development of T2DM, while often overlooked, individuals with a normal BMI (18.5-24.9 kg/m) can face a heightened diabetes risk. As weight increases, moving from overweight (25-29.9 kg/m) to obese (>30 kg/m), the likelihood of developing T2DM rises sharply, underscoring the importance of maintaining a healthy weight to mitigate this risk.[10]

The HbA_{1c} testing of the blood which provides insight on blood sugar levels in periods of three months is a valuable tool not only in the diagnosis but also the management of diabetes. The life span of red blood cells is 90 days and their use has been to assess the proportion of glycated haemoglobin where glucose regulation is depicted in a time dimension. Percentage results achieved in blood sugar control are then used to make decisions concerning the treatment plan of the patient or to evaluate the effectiveness of the treatment over time.[11]

All people with type 2 diabetes experience high reluctance in increasing even a little HbA_{1c} levels which significantly translates in poor outcome, increase total mortality by 30% and cardiovascular and ischemic heart disease by 40%.[12]

Insulin is considered one of the cornerstones for achieving good glycemic control among patients with T2DM. It is important that insulin therapy be initiated in a timely manner to preserve beta-cell function, reduce toxic effects of hyperglycemia, and enhance beta-cell recovery. In this regard, by minimizing the pressure on beta cells, insulin exerts an anti-apoptotic effect, preserving beta-cell functional integrity. Early insulin therapy has also been demonstrated to delay or reverse beta-cell dysfunction, whereas short-term treatment increases sensitivity to insulin, reducing insulin resistance and thereby enhancing glucose metabolism in general.[13]

The body maintains blood levels of glucose when fasting through the continuous production of basal insulin, whereas blood glucose after meals is maintained through a dual mechanism, the activities of continuous basal insulin secretion, as well as meal-stimulated bolus insulin release. Insulin therapy for T2DM patients involves a host of preparations, each with its unique profile that meets specific needs. However, if administered improperly, the consequences can lead to serious, life-threatening blood sugar swings and even DKA.[14]

Insulin errors in one study were noted to have hypoglycemia visits related to dosing errors, mix-ups involving insulin products, or mistaken timing with meals; thus, proper administration was an important factor.[15]

There are various kind of complications has been observed with the patients diagnosed with the T2DM. some of the common complications which was noticed during the study were as:

Hypoglycemia is the condition where the plasma glucose concentration drops between 50-70 mg/dL, requiring immediate intervention. Any impairment in counter-regulatory responses or being unaware of sugar level and eventually use of improper doses of insulin contributes to hypoglycemia.[16] Hyperglycemia can be defined as elevated blood sugar levels, above 125-180 mg/dL 2 hr postprandial. Factors like reduced insulin secretion, increased glucose production and ineffective utilization of glucose along with the wrong dose of insulin administration can result in hyperglycemia. This serves as a precursor to the onset of microvascular and macrovascular complications.[17]

Diabetic peripheral neuropathy has been reported as the most common complication associated with diabetes. Disruption in neuropeptide expression, degrading of essential structural proteins/neurotrophic receptor functions, and hyperactivation of the AGE-RAGE signaling axis can exacerbate oxidative stress leading to peripheral disease.[18] Research has shown that insulin treatment can sometimes make diabetic retinopathy worse. This might be because insulin can work with a protein called vascular endothelial growth factor to cause new blood vessels to grow in the retina, making the condition worse. It affects about one-third of people with diabetes. The condition may lead to either proliferative diabetic retinopathy, where new blood vessels grow abnormally or diabetic macular oedema, where fluid builds up in the central part of the retina.[19,20]

Diabetic emergencies, such as Diabetic Ketoacidosis (DKA), are precipitated by a triad of factors: dehydration, hyperglycemia, and metabolic acidosis, stemming from excessive ketone production. The pathophysiological mechanisms underlying ketoacidosis involve a severe deficiency of insulin, coupled with an overproduction of counter-regulatory hormones, including glucagon, catecholamines and cortisol. This hormonal imbalance triggers a cascade of events, culminating in hyperglycemia and the accumulation of ketone bodies, comprising acetoacetate, 3-beta-hydroxybutyrate and acetone.[21]

Lipo-hypertrophy is clinically significant complication of insulin therapy, characterized by a localized, rubbery swelling in the subcutaneous tissue at the injection site. This adverse reaction is precipitated by the lipogenic effects of insulin and/or trauma associated with repeated injections, leading to an increased risk of glycemic variability and higher insulin dose requirements. Insulin treatment is associated with a range of cutaneous alterations and skin-related adverse effects with lipo-hypertrophy being a notable example of a localized, insulin-induced lipogenic response.[22]

MATERIALS AND METHODS

Study design

A 6-month prospective observational study was conducted at the general medicine Department of a tertiary care hospital in Bangalore to evaluate the effectiveness of the insulin used in

the patients diagnosed with the T2DM. The study included 106 patients were included in the study among which 89 were on insulin and other 17 were not on insulin. Demographic details and medical history were collected and recorded in a specially designed data collection form. The prescriptions were carefully assessed to identify and evaluate the pattern of insulin prescribed, providing insights into the management of T2DM.

The sample size was fixed at 106 patients, taking into account several factors. Feasibility of recruiting patients within the 6-month timeframe, resource constraints such as data collection capacity were considered. The desired level of statistical power to ensure precise and confident results and insights from previous studies on breast cancer patients were taken into consideration to estimate the required sample size. By utilizing Cochran's formula, it was determined that 106 patients would provide a representative and manageable dataset to achieve the study objectives while ensuring feasibility and validity.

RESULTS

Diabetic mellitus is a leading metabolic disorder worldwide, where insulin has played a crucial role in the treatment of T2DM. This study aims to evaluate the demographic profile, clinical findings, and prescribing patterns of the insulin among the study population. This prospective observational study was conducted at a tertiary care hospital in Bangalore over a period of 6 months. 106 patients diagnosed with T2DM and 89 receiving insulin and other 17 were not on insulin. Demographic data, clinical findings, and prescribing patterns were collected and analysed. The study findings are as follows.

The study cohort comprised a total of 106 patients, with males (*n*=55, 51.88%) and females (*n*=51, 48.11%). A comprehensive assessment of patient's understanding of diabetes revealed a notable 60.37% (*n*=64) of patients demonstrated satisfactory knowledge of diabetes, its associated comorbidities, and long-term complications, whereas 39.62% (*n*=42) exhibited a suboptimal understanding, highlighting a significant gap in awareness and medication utilization.

An analysis of patients' responses concerning their medication use revealed a notable variance in weight management outcomes, wherein a majority of patients (*n*=64, 60.37%) achieved weight loss, while a smaller proportion (*n*=16, 15.09%) experienced weight gain, and a significant percentage (*n*=26, 24.52%) successfully maintained a stable weight.

The study entailed providing comprehensive counselling to patients (*n*=79) on various crucial aspects, including insulin therapy (benefits, dosing, potential problems, and side effects), proper use of syringes and pens, and the characteristics of different insulin types. Additionally, patients with comorbidities such as neuropathy and diabetic foot were educated on leg hygiene, while all patients received guidance on nutrition, beneficial foods, fruits to avoid, and the significance of medication adherence. Furthermore, the importance of regular physical activity was emphasized. However, a notable proportion of patients (24.52%, *n*=26) encountered certain obstacles, including language barriers,

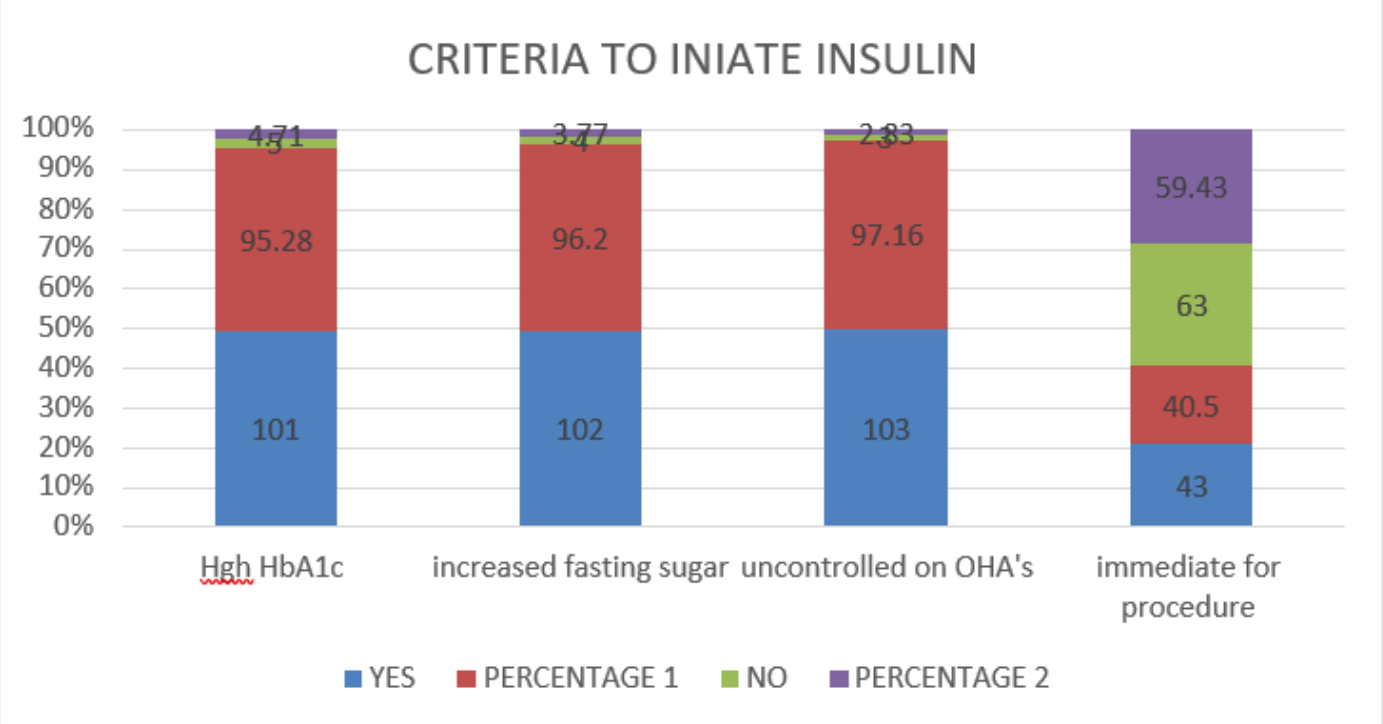

Figure 1: Graphical representation of criteria to initiate insulin therapy.

Table 1: Socio-Demographic Data (*n*=106).

Demographic details	Patient distribution	Sample (*n*=106)	Percentage %
Age	30-39	3	2.83%
	40-49	9	8.49%
	50-59	35	33.01%
	60-69	25	23.58%
	70-79	27	25.47%
	80-89	4	3.77%
	Above 90	3	2.83%
Gender	Male	51	48.11%
	Female	55	51.88%
Smokers	Yes	35	33.01%
	No	71	66.9%
Alcoholic	Yes	35	33.1%
	No	71	66.9%
Weight assessment	Lost	64	60.37%
	Gained	16	15.09%
	Maintained	26	24.52%
Insulin therapy	Initially on insulin	89	83.96%
	Not on insulin initially	17	16.03%

Table 2: Knowledge Assessment.

Questions	Knowledge assessment	Sample (*n*=106)	Percentage %
1. Patient understanding	Good	64	60.37%
	Poor	42	39.62%
2. Methods of administration	Syringe	55	51.88%
	Pen	23	21.69%
	Syringe + Pen	18	16.98%
3. Site of administration	Thigh	48	45.28%
	Stomach	78	73.58%
	Shoulder	48	45.28%
4. Challenges associated	Lipohypertrophy	31	29.24%
	Anxiety to prick	62	58.49%
	Forgetting	55	51.88%
	Pain	56	52.83%
5. Physical activity	Performed	68	64.15%
	Not performed	38	35.84%
6. Patient counselling	Provided	79	74.52%
	Not provided	27	25.47%
	Barriers	26	24.52%
	No barriers	80	75.47%

lack of interest, time constraints, and reluctance to engage in counselling sessions.

Figure 1 illustrates the criteria for initiating insulin therapy among the patients, revealing that an overwhelming majority (*n*=101, 95.28%) had elevated HbA_{1c} levels. Insulin therapy was prompted by elevated fasting blood glucose levels in 96.2% (*n*=102) of patients, while 97.16% (*n*=103) required insulin due to the ineffectiveness of oral antidiabetic medications in achieving adequate glycaemic control. Furthermore, insulin was prescribed for 40.5% (*n*=43) of patients undergoing immediate surgical procedures to mitigate blood glucose fluctuations, highlighting

Table 3: **Distribution of prescribing pattern of insulins.**

Type of insulin	Name of insulin	No. of patients	Percentage
Rapid-acting insulin	Insulin Aspart	4	3.77
Ultra-long-acting insulin	Insulin Degludec	1	0.944
Long-acting insulin	Insulin Lantus	36	33.96%
Short-acting insulin	Insulin human Actrapid	38	35.84%
Premixed insulin	Insulin human Mixtard	27	25.47%

Table 4: **Table describing optimization of insulin dosing units.**

Blood sugar level (mg/dL)	Low dose scale (units)	Moderate dose scale (units)	High dose scale (units)
< 70	2	0	0
70-130	2	4	8
131-180	4	6	8
181-240	4	6	8
240-300	6	8	10
301-350	6	8	14
351-400	8	10	14
>400	10	16	20

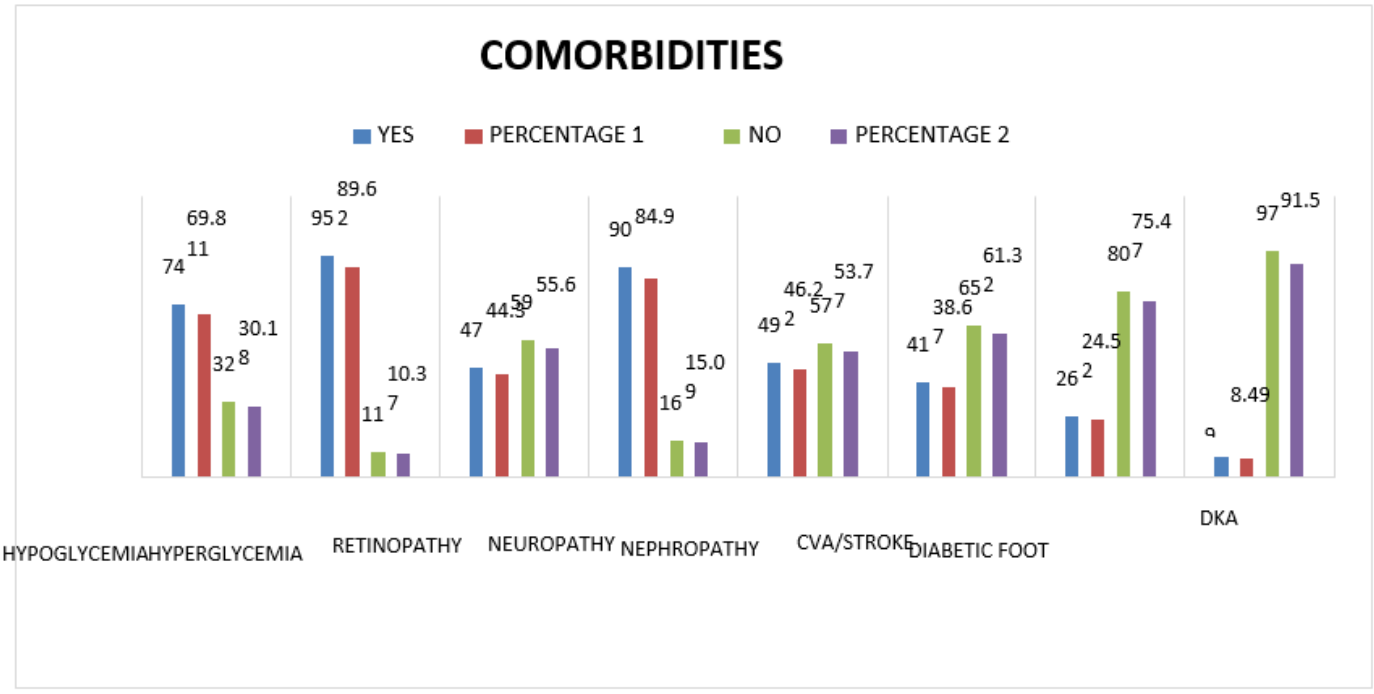

Figure 2: Graphical depiction of comorbidities presenting in diabetes patients.

the critical role of insulin therapy in managing acute glycaemic variability in the hospital setting.

Figure 2 illustrates the diverse comorbidities prevalent among the study population, revealing a high incidence of hypoglycaemic events in 69.81% (*n*=74) of patients, while hyperglycaemia was an even more pervasive issue, affecting 89.62% (*n*=95). Diabetic retinopathy was diagnosed in 44.3% (*n*=47) of patients, and diabetic neuropathy emerged as the most common comorbidity, impacting 84.9% (*n*=90) of the study population. Additionally, diabetic nephropathy was reported in 46.22% (*n*=49) of patients, and cardiovascular complications, including CVA/stroke, were present in 38.67% (*n*=41) of cases. Diabetic foot was another significant comorbidity, affecting 24.52% (*n*=26) of patients,

although diabetic ketoacidosis was relatively less common, occurring in 8.49% (*n*=9) of the study sample.

The patient's blood glucose levels guided the customization of their insulin regimens, with varied dosing approaches implemented. Notably, Insulin As part was prescribed for a select few (*n*=4), while Insulin Degludec was administered to one patient (*n*=1) for an urgent procedure. The majority of patients (*n*=36) relied on long-acting Insulin Lantus as their daily staple, whereas Insulin Human Actrapid (*n*=38) was employed with flexible dosing to accommodate unique individual requirements. Furthermore, Premixed Insulins were tailored for 27 patients, underscoring the personalized nature of insulin therapy in this study.

DISCUSSION

This observational study consisting of 106 participants, determines that predominance of T2DM belongs to 50-59 years, as presented in Table 1. This remarks age is a considerable factor due to deficiency in insulin secretion and growth in insulin resistance, thus impairing carbohydrate metabolism and energy homeostasis according to a study done by Katarzyan *et al.*[23]

Research done by *Liang Shi et al.*, elucidated a complex dynamic between alcohol intake and the onset of T2DM, revealing that temperate consumption may confer a protective effect, whereas excessive smoking precipitates a heightened risk. Specifically, a moderate drinking pattern, characterized by a weekly intake of 1-3 drinks, is associated with enhanced insulin sensitivity and a reduced likelihood of developing T2DM. Conversely, tobacco use particularly more than 20 cigarettes per day and cumulatively exceeding 40 pack-years, is a significant predictor of T2DM incidence.[24]

As shown in Table 1, Entirely 83.96% of individuals, comprising 106 subjects, were commenced on initially insulin therapy whereas smaller proportions of 16.03% of patients did not necessitate insulin therapy.

Table 2 shows the knowledge of the patients regarding insulin regimen, where *n*=42 (39.62%) population had a poor understanding that might relate to non-adherence, giving rise to unknown complications and inappropriate use of insulin.

To accommodate inter-subject variability, a multi-method approach proved advantageous in terms of cost-effectiveness, safety, and convenience with the choice of method contingent upon the specific type of insulin administered. The data revealed that syringes were predominantly employed for the administration of regular, intermediate-acting and premixed insulins, whereas insulin pens were typically utilized for long-acting insulins. Notably, pens offered enhanced benefits, including reduced pain, convenient dosing, improved safety and precise glycemic control, whereas syringes presented a more cost-effective and readily accessible alternative. A study conducted by Bastian *et al.* highlighted the clinical and economic disparities between insulin pens and traditional vials/syringes, concluding that pens facilitated improved adherence and diminished hypoglycemic episodes, while syringes offered economic advantages in terms of reduced costs and convenience.[25]

Individuals' anticipation regarding insulin administration was intensified by their anxiety, concerning the risk of hypoglycemia, dosing inaccuracies due to visual impairments and fear of injection pain. Additionally, some participants struggled with recalling prescribed dosages. A study by *Giuseppe Naria Rozzeroli et al.* identified LH as a significant dermatological complication of insulin therapy in 31 cases. The development of LH was strongly correlated with inadequate injection site rotation and failure to alternate injection sites, with prolonged insulin use and multiple daily injections further contributing to its onset. The presence of LH increased the likelihood of severe hypoglycemia by 2.7 times. Therefore, rotating injection sites is crucial to prevent complications such as infection, impaired insulin absorption and LH.[26]

In the study, *n*=68 subjects performed physical activity, engagement in physical activity enhances the body's insulin sensitivity facilitating augmented glucose uptake by active muscle cells and maintaining a delicate balance in hepatic glucose production. As physical intensity escalates, the body increasingly relies on carbohydrates to fuel muscular activity, thereby optimizing glucose metabolism. Research has demonstrated that regular participation in moderate-intensity activities, such as walking and vigorous exercise, contributes significantly to the mitigation of T2DM.

Figure 1 represents the criteria for initiating insulin therapy, where out of 106 patients, a 95.28% exhibited impaired HbA_{1c} levels, while 96.2% consistently demonstrated elevated fasting blood glucose levels surpassing 300mg/dl. Moreover, 97.16% of patients required insulin initiation due to suboptimal glycemic control or poor adherence to OHAs.

The findings suggest that when glucose uptake by cells is impaired, leading to elevated blood glucose concentrations, insulin's ability to facilitate glucose uptake is hindered, resulting in insulin resistance. If left untreated, this condition precipitates a vicious cycle of escalating insulin levels, increased RBC stickiness and concomitant rises in HbA_{1c} levels.

Crucially, elevated HbA_{1c} levels correlate directly with disease progression and the development of long-term complications affecting the eyes, kidneys, heart, and feet. In this context, insulin therapy emerges as a crucial intervention for mitigating further damage and halting disease progression.

As per Table 3, current study comprising 106 patients with diverse blood glucose concentrations, personalized insulin regimens were implemented, featuring varying doses of short-acting Human Actrapid insulin administered via a sliding

scale protocol. Blood glucose levels were meticulously monitored at 4-hr intervals (Q4) to ensure precise dosing.

The study employed a tiered dosing approach, encompassing low, moderate, and high dose scales, with increments ranging from 2 units to 20 units as per shown in Table 4. The dosing strategy was tailored to individual patient needs, considering concomitant OHAs, medical procedures and the imperative for prompt blood glucose control.

The low dose scale was preferred for maintaining normoglycemia, while the moderate dose scale was employed for enhanced glycemic control to prevent potential complications. The highest dose scale was reserved for targeting specific clinical scenarios. A direct proportional relationship was observed between blood glucose levels and insulin dosing, underscoring the importance of personalized insulin therapy in achieving optimal glycemic control.

CONCLUSION

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder, and insulin therapy constitutes a fundamental component of effective disease management. This observational study conducted in tertiary care hospitals assessed the efficacy of insulin therapy, elucidating its pivotal role in modulating blood glucose concentrations and mitigating associated complications. The findings underscore the imperative of timely insulin initiation to optimize clinical benefits, as well as the necessity for individualized insulin analogue selection to achieve optimal glycemic control.

A significant positive correlation was observed between advancing age and the development of diabetes and insulin resistance, highlighting the importance of early intervention. Furthermore, insulin administration strategies and patient adherence to treatment regimens exert a profound impact on the quality of life in diabetes patients. The study demonstrated that targeting blood glucose levels through insulin therapy significantly reduces morbidity and mortality rates, underscoring the critical role of glycemic control in diabetes management.

Notably, the study identified smoking and comorbidities as salient factors contributing to impaired blood glucose control, emphasizing the need for comprehensive risk factor management. Common complications in diabetic patients, including hypoglycemia, hyperglycemia, diabetic neuropathy, and diabetic nephropathy, were also observed, highlighting the importance of vigilant monitoring and management. The use of sliding scale insulin in the hospital setting demonstrated efficacy in achieving glycemic control, with appropriate dosing scales and adjunctive long-acting insulin (Lantus) therapy.

Through patient education and counselling, the study addressed knowledge gaps and promoted physical activity, underscoring the importance of a multidisciplinary approach to diabetes management. Ultimately, this study reinforces the critical role of insulin therapy in type 2 diabetes management and emphasizes the need for personalized treatment strategies to optimize clinical outcomes and improve patient-centered care.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 diabetes millets; **HbA_{1c}:** Glycolate haemoglobin; **OHAs:** Oral hypoglycemic agents; **RBC:** Red blood cell; **Q4:** 4-hr intervals; **LH:** Lipo hypertrophy; **DKA:** Diabetic Ketoacidosis.

LIMITATIONS

While this study provides valuable insights, its observational nature necessitates an acknowledgement of its limitations, including:

The study's single-center design constrained the sample size, potentially limiting the generalizability of the findings.

A study duration of six months may not have captured the full spectrum of outcomes, potentiating introducing temporal biases.

Lack of consistent follow-up among discharged patients lacks completeness of the data.

Patient disengagement and reluctance to provide personal and past information hindered data quality and completeness.

The self-reported nature of the data introduces potential biases, as the accuracy and reliability of participant responses cannot be assured.

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