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Original Article

Comparison of thrice-daily premixed insulin with a basal-bolus regimen in Iraqi patients with insulin-dependent diabetes

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Abstract

The use of basal-bolus therapy is common in Iraq, yielding positive results in terms of glycemic control but often leading to poor patient satisfaction and compliance due to the increased number of required injections. There is a need for an alternative insulin regimen that maintains efficacy and safety comparable to the basal-bolus protocol while offering greater convenience. Unlike in Western communities, premixed insulin is more widely utilized and accepted among Iraqi patients. The study compares the effectiveness of thrice-daily premixed insulin therapy with the basal-bolus regimen in patients with insulin-dependent diabetes. In a prospective, non-randomized, controlled interventional trial, 25 patients previously using a basal-bolus regimen were transitioned to thrice-daily premixed human insulin. The primary outcomes assessed were changes in HbA1c levels, and secondary outcomes included differences in daily self-monitored blood glucose (SMBG) readings, the number of hypoglycemic events, weight changes, and overall patient satisfaction. The mean HbA1c level in patients when on the basal-bolus protocol was 8.828, which decreased to 8.7 after three months of switching to thrice-daily premixed insulin (a mean difference of -0.179±0.09, with a p-value<0.0001). The mean number of weekly hypoglycemic events remained similar between the basal-bolus regimen (1.44 events) and the premixed insulin regimen (1.48 events). Furthermore, 65% of the patients expressed satisfaction with the results of the new treatment protocol, and 75% found it to be easier and more convenient. Thrice-daily premixed insulin therapy is deemed non-inferior to the basal-bolus regimen when patients require intensification of their insulin therapy, as it maintains glycemic control and hypoglycemic event frequency while offering the advantages of improved patient convenience and compliance.

Keywords: insulin, diabetes mellitus, premixed insulin, basal-bolus regimen.

Abbreviations: SMBG – Self-Monitored Blood Glucose; HbA1c – Glycated Hemoglobin; TDD – Total Daily Dose; TID – Three Times Daily.

Introduction

Diabetes Mellitus is a chronic disease that occurs when the pancreas does not produce enough insulin or when there is insulin resistance in the peripheral tissues. Insulin is a hormone that controls the process of gluconeogenesis and glycogenolysis. When the blood levels of insulin decrease or insulin cannot work effectively, hyperglycemia occurs, leading to progressive serious damage to many organs, such as the eyes, heart, kidneys, and feet.in 2014, it was estimated that 8.5% of adults older than 18 years had diabetes. In 2019, diabetes was the leading cause of 1.5 million deaths, and 48% of mortality due to diabetes occurred before the age of 70 years. Another 460,000 deaths due to renal failure were caused by diabetes, and hyperglycemia caused nearly 20% of cardiovascular deaths [1].

Symptoms of diabetes may develop suddenly, classically in type 1 diabetes, but in type 2 diabetes, the symptoms can be milder and may take many years to be

reported. The symptoms include polyuria, polydipsia, blurred vision, increasing tiredness, and unintentional weight loss [2].

Type 1 diabetes mellitus (T1DM) results from destroying the pancreatic beta cells responsible for producing insulin, leading to insulin deficiency. The destruction of beta cells is usually the result of an autoimmune process. However, it can be due to genetic disorders such as cystic fibrosis or viruses that infect the pancreas, such as mumps. T1DM was initially believed to develop mainly during childhood or adolescence, but it can occur even in patients older than 80 [3]. The diagnosis of T1DM may be challenging as it may be misdiagnosed as type 2 diabetes mellitus (T2DM) in adults. Latent autoimmune diabetes in adults (LADA), a subtype of T1DM that involves a slowly progressing immune-mediated loss of beta cells, may comprise 5–15% of T2DM cases. Diagnosis of T1DM is extremely important because these patients need to receive immediate insulin therapy to prevent the onset of diabetic ketoacidosis, which is a potentially life-threatening condition, and to delay the microvascular and macrovascular complications [4].

The usual starting protocol for premixed insulins (biphasic insulin Aspart 70/30, biphasic insulin Lispro 75/25, or regular/NPH 70/30) still cited in medical textbooks and used in general practice is to give the patient two-thirds of the total daily insulin dose in the morning before breakfast and one-third in the evening before dinner [5, 6]. Doctors in general medical practice settings may be less likely to use ratios other than two-thirds/one-third because of worries about the safety and efficacy of a regimen that does not follow this usual approach. However, it is difficult to find practical evidence to guide healthcare providers regarding the use of a different premixed insulin regimen [7].

The most recent guidelines for diagnosing T1DM are similar to those for T2DM. The guidelines of the American Diabetes Association (ADA) and the UK National Institute for Health and Care Excellence (NICE) do not recommend routinely testing C-peptide or autoantibodies for diagnosis and categorization of diabetes. However, these could be used in clinically indeterminate cases. Considering the natural history of Type 1 DM, the development of type 1 diabetes was proposed to pass through three stages: stages 1 and 2 are both asymptomatic with detectable beta cell autoimmunity and dysglycemia (impaired fasting glucose or impaired glucose tolerance), and stage 3 is symptomatic with new-onset hyperglycemia [8, 9].

American Diabetes Association (ADA) and Chinese Diabetes Society (CDS) guidelines recommend a glycemic target of HbA1c <7.0% in most patients with T2DM. Achieving this target requires controlling both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) [10]. Furthermore, when treatment intensification is necessary, it is recommended that it is started early to decrease the risk of short- and long-term complications from diabetes. Indeed, it has been shown that patients with T2DM and HbA1c ≥7.0% who did not intensify treatment within 1 year had a significantly higher risk of acute coronary syndrome and cerebrovascular accidents compared with those who intensified treatment [11].

Basal insulin, such as the long-acting insulin analogs Insulin Detemir, insulin Glargine, and Degludec, dosed once daily, is recommended by the ADA and CDS as initial insulin therapy. However, for patients who

Table 1: Changes in mean SMBG readings of patients on basal-bolus insulin before switching to thrice daily premixed insulin.

Blood sugar reading time	Mean readings on Basal bolus regimen	Mean readings on Thrice daily premixed insulin	Change in mean readings	Standard deviation	Confidence interval	P-value
FBS	110	112	2	1.414±1	1.959–2.8	<0.0001
2hr after breakfast	150	120	-30	21.213±15	-42.0637–17.93	<0.0001
2hr after lunch	150	180	30	21.213±15	17.93–42.06	<0.0001
Pre-dinner	250	210	-40	8.284±20	-56.08–23.91	<0.0001
2hr after dinner	180	150	-30	21.2132±15	-42.06–17.93	<0.0001
Bedtime	165	100	-65	45.961±32.5	91.137–38.86	<0.0001
3 a.m.	100	120	20	14.1421±10	11.95–28.04	<0.0001

do not reach glycemic targets using only basal insulin, studies have revealed that biphasic insulin Aspart 30 (BIAsp 30), which is premixed insulin that includes both rapid-acting soluble insulin Aspart (30%) and intermediate-acting protamine insulin Aspart (70%) in one formulation, given twice daily (BID) can be used to improve glycemic control [12].

CDS guidelines state that premixed insulin administered twice daily can be used either to start or intensify insulin treatment [13].

Both three-times daily and Twice-daily premixed insulin regimens are effective and safe. However, real-world comparative head-to-head data are lacking, and it is possible that dividing the dose among three meals may be of further benefit to some patients in the form of a lower risk of hypoglycemia. Therefore, the current trial aimed to compare the safety and effectiveness of Premixed insulin 70/30 three times daily with the conventional twice-daily protocol [14, 15].

This study compares the basal-bolus regimen with premix insulin analogs regarding glycemic control, frequency of hypoglycemic events, weight changes, and patient preferences and convenience.

Material and methods

Patients

Twenty-five patients with diabetes mellitus dependent on insulin therapy on a basal-bolus regimen were changed to thrice daily premixed insulin (Mixtard vials or Novomix pens in the dose of 1 unit/kg in three equally divided doses). Their SMBG profile, HbA1c, and body weight data were obtained before and 3 months after changing their treatment protocol. Weekly follow-up appointments were set to assess patient compliance, overall and nocturnal hypoglycemia episodes, and SMBG readings.

Exclusion criteria

- Patients on oral hypoglycemic medications in the past 3 months;
- Pregnant and lactating patients;
- Use of medications or herbal preparations that might affect the weight.

Study design

This is a randomized controlled clinical trial (RCT) interventional study. The primary outcome was the change in HbA1c over the study period (12 weeks), while the secondary outcome was fasting and postprandial glucose excursions, frequency of hypoglycemic events, weight changes, and overall treatment satisfaction.

Statistical analysis

Changes in blood glucose readings, HbA1c, body weight, and frequency of hypoglycemia (nocturnal and overall) were analyzed using a logistic regression model,

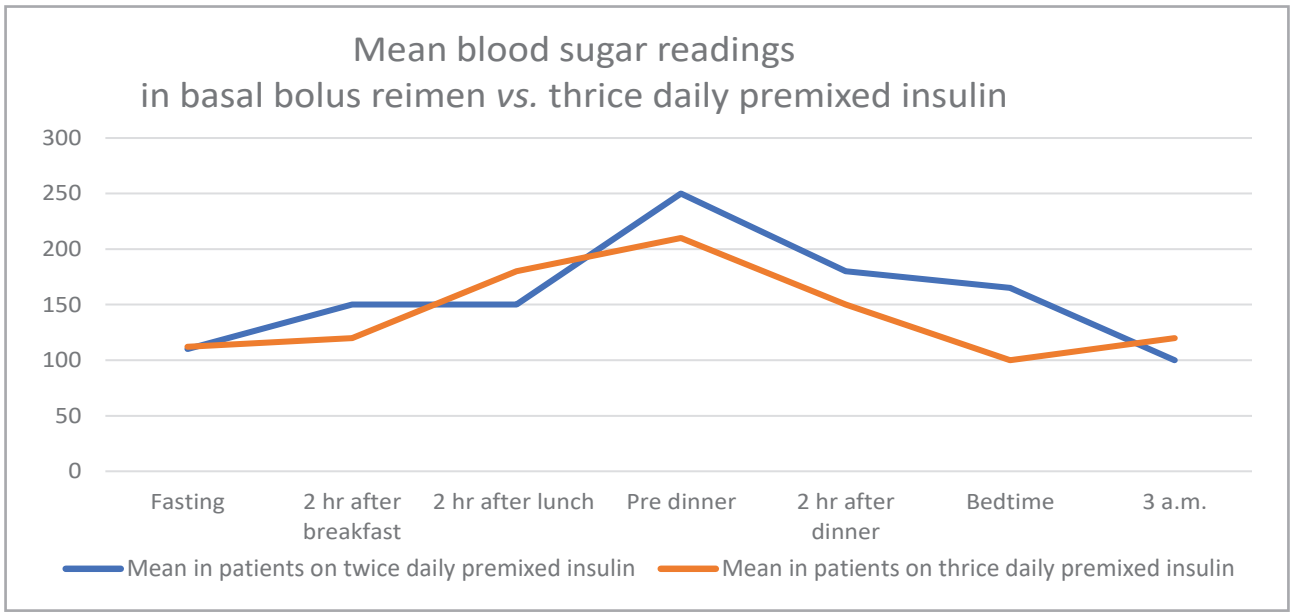

Figure 1: Mean blood sugar readings in patients on basal-bolus regimen before and after switching to premixed insulin.

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and a p-value<0.05 was considered statistically significant. Analysis was done using SPSS 15

Results

Changes in SMBG

Mean changes of the blood glucose readings (7 points SMBG: fasting blood glucose, 2 hours after breakfast, 2 hours after lunch, pre-dinner, 2 hours after dinner, bedtime, 3 a.m. blood glucose readings) were plotted on both regimens (basal-bolus insulin *versus* thrice daily premixed insulin).

Thrice-daily premixed insulin was found to be non-inferior to the basal-bolus regimen in terms of glycaemic control, with better blood sugar control in the afternoon (Table 1).

Charts of patients using premixed insulin show a more uniform and steady curve than those obtained using the basal-bolus regimen (Figure 1).

Changes in HbA1c

The mean HbA1c in the patients while they were on basal-bolus insulin was 7.82±0.09, which decreased to 8.7±0.09 (confidence interval 95% -0.179–0.0768, p-value <0.0001 (statistically significant) (Figure 2).

Incidence of hypoglycemia

Patients on basal-bolus insulin had a mean number of overall hypoglycemic episodes of 1.44±0.02, which changed to 1.48±0.02, confidence interval 95% 0.02–0.05, p-value<0.0001, while the incidence of nocturnal hypoglycemia changed from the mean of 0.6±0.02 in patients on a basal-bolus regimen to 0.56±0.02 in patients on thrice daily premixed insulin, confidence interval -0.05–0.028, p-value<0.0001. Results are emphasized in Figure 3 and Figure 4.

Weight changes

The mean body weight at the end of the study did not significantly change after using premixed insulin compared to a basal-bolus regimen (63 *versus* 65 kg, p-value 0.15), as weight changes are a major concern among patients (Figure 5).

Patient preferences

Regarding ease of use, 75% found premixed insulin easier, 10% thought it was the same as a basal bolus, and 5% thought it was more difficult. Regarding cost-effectiveness, 65% thought it was more cost-effective, 33% thought it was the same, and 12% thought it was more expensive. Regarding overall satisfaction with the results, 65% were satisfied, 33% thought it was the same, and 12% preferred the basal-bolus regimen.

Discussion

There are many internationally recognized recommendations for initiating and intensifying insulin therapy using premixed insulin. However, these

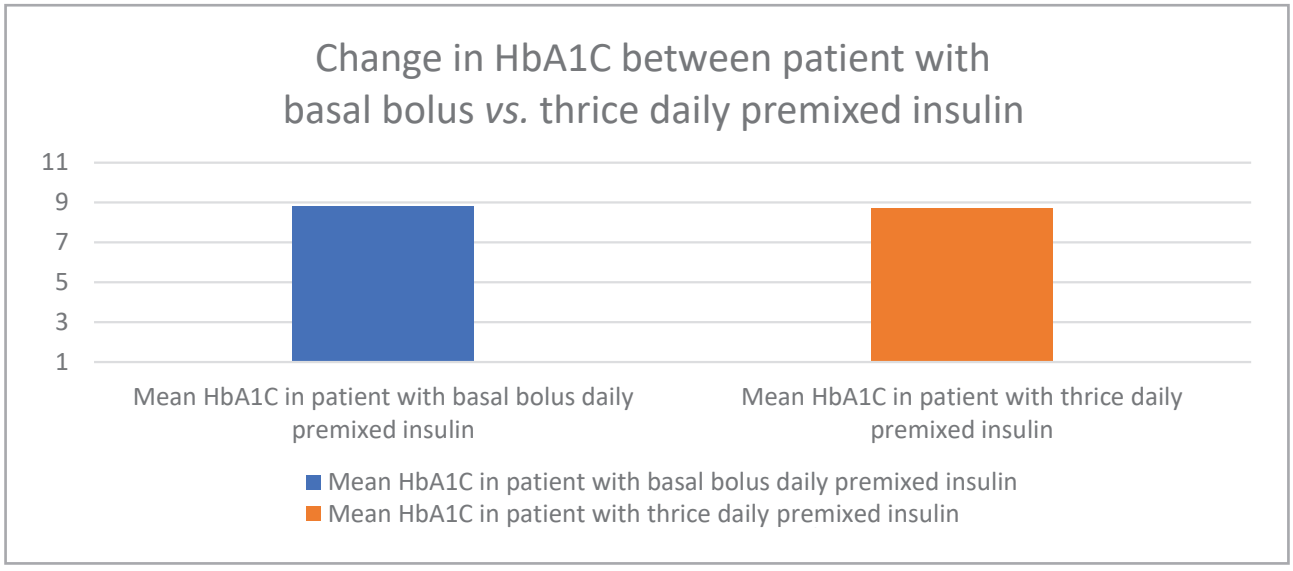

Figure 2: Change in mean HbA1c before and after changing from basal-bolus regimen to premixed insulin.

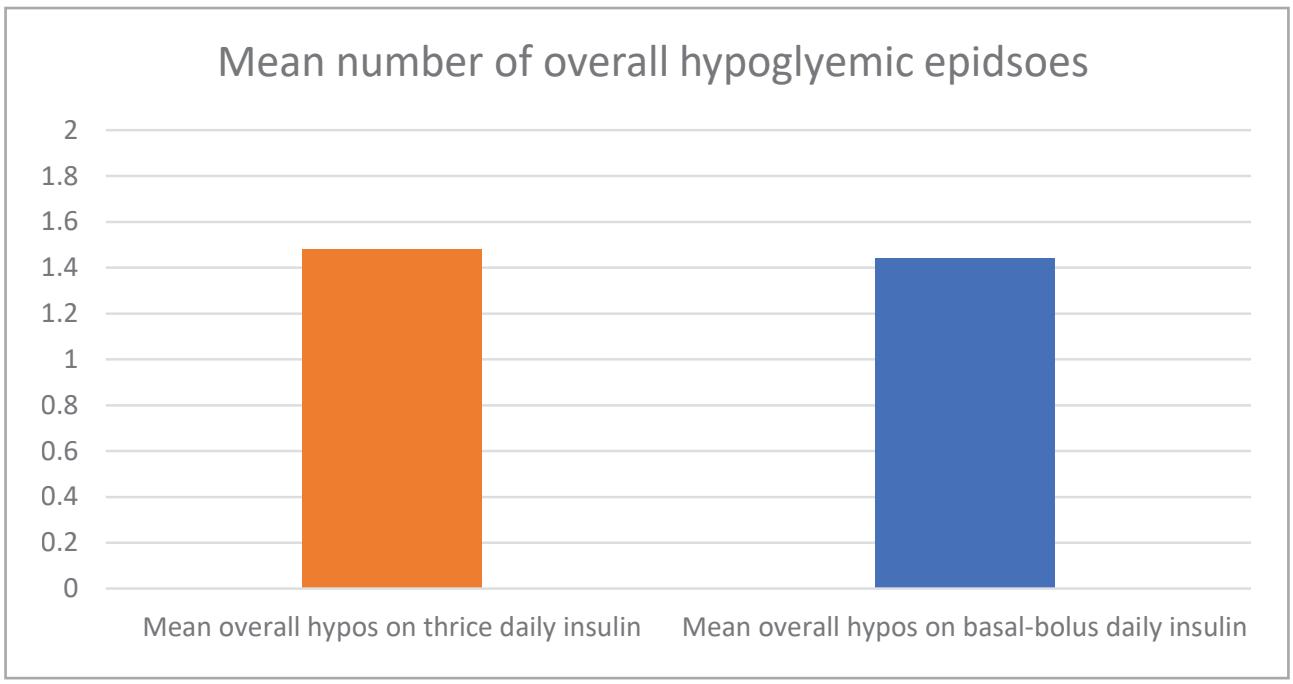

Figure 3: Mean number of overall hypoglycemic episodes in patients on basal-bolus *versus* premixed insulin.

guidelines do not compare premixed insulins with other types of insulin preparations. Furthermore, they do not specifically describe the patient characteristics that are more suitable for premixed insulins. This study aims to identify gaps in current clinical practices and establish an objective, evidence-based approach to selecting patients more suitable for premixed insulins.

Premixed insulins are fixed combinations of rapid- or short-acting and intermediate- or long-acting insulins for both fasting and postprandial glycemic control. Depending on patient requirements, they can be dosed once, twice, or thrice daily. Premixed insulin has drug pharmacokinetics that provides 24-hour efficacy and patient convenience. This may explain the better adherence and improved glycemic control associated with premixed insulins. The conventional premixed biphasic human insulin is a combination of regular human insulin and neutral protamine Hagedorn (NPH)

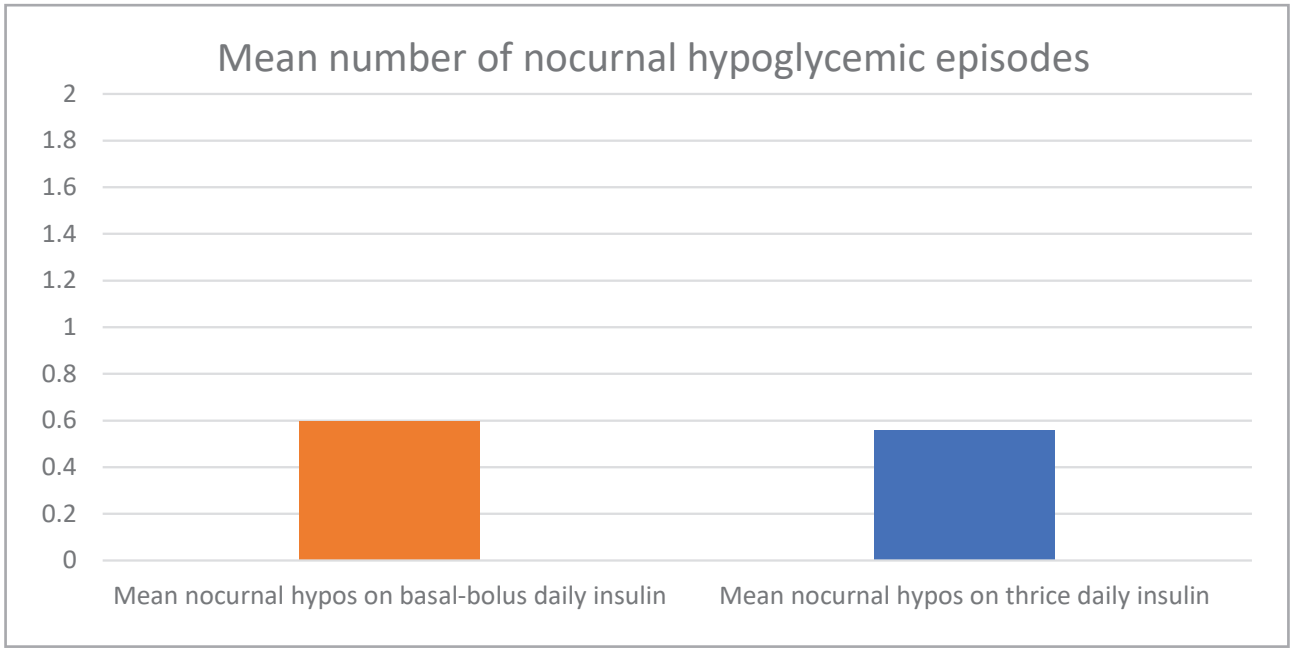

Figure 4: Mean number of the nocturnal episodes of hypoglycemia in patients on basal-bolus regimen *versus* premixed insulin.

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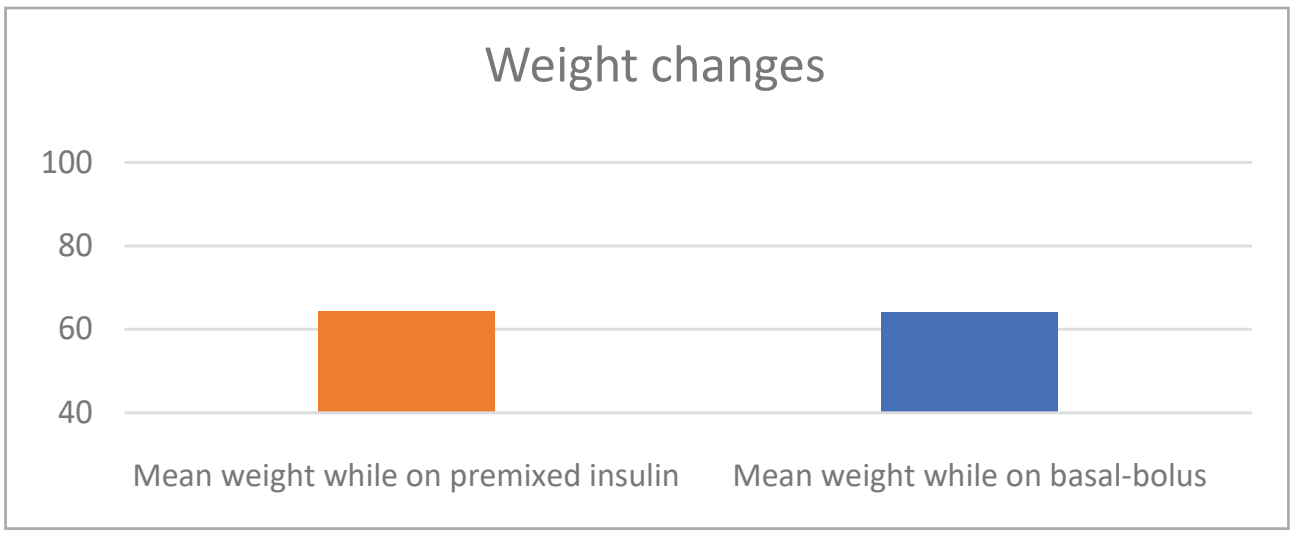

Figure 5: Difference in body weight while on basal-bolus and premixed insulin.

in the ratio of either 30/70 (more widely available and used) or 50/50. These are administered half an hour before meals, and the action lasts for approximately 10–16 hours, but in clinical practice, their maximal effect diminishes after 6–8 hours [16].

In a study comparing premixed and basal plus regimens, Downie *et al*. found that both regimens have similar efficacy and safety for insulin initiation in insulin-naïve patients and intensification in patients who have not been properly controlled on basal insulin [17]. In a meta-analysis of 13 randomized controlled trials (16–60 weeks; n=5255) comparing premixed and basal-bolus regimens, there were no significant differences in HbA1c levels, the rate of hypoglycemia, weight change, or daily insulin dose between the two regimens, despite the latter's more complex approach and higher number of daily injections [18].

The Indian National Consensus Group (INCG) published guidelines for starting and intensifying treatment with premixed insulin in the primary care management of diabetes. According to INCG, patients with insulin-dependent diabetes for whom a basal-bolus regimen is not practical or achievable can benefit from premixed insulin in two or three daily doses, with similar efficacy and simplicity. This approach should be considered at all stages of diabetes treatment. The Royal Australian College of General Practitioners (RACGP) has also provided guidelines for initiating, up-titration, and intensifying therapy with premixed insulin. According to these guidelines, premixed insulin may be an appropriate and simple option for blood sugar control when fasting and postprandial glucose levels are consistently elevated. Patients may be switched to premixed formulations if HbA1c target levels cannot be achieved using only basal insulin or when insulin therapy is intensified to basal plus or basal-bolus. It is important to emphasize the importance of proper nutrition and physical activity at all stages of treatment initiation and intensification [19, 20].

The main patient characteristics that directly affect the choice of therapy with premixed insulin include the duration of diabetes, overall health, other comorbidities, previous and current treatment, patient's lifestyle, and preferences. Asians have higher postprandial blood glucose levels due to the higher carbohydrate content of their meals. The West African diet is carbohydrate-rich, resulting in elevated postprandial blood glucose readings. Premixed insulin formulations are preferred in Southeast Asia and Africa and are included in the National List of Essential Medicines of many countries [21].

Premixed insulin is a better choice for patients with non-compliance problems because they are unwilling or struggling to adhere to the increased injections and close monitoring required with basal plus/basal-bolus regimens. As part of a patient-centered approach to managing diabetes, patient-reported outcomes should be measured before and during treatment. Quality of life is an important measurable target that can be used to assess the outcomes of insulin regimens. Other potential outcomes include patient satisfaction, anxiety and depression, and coping skills [22].

There are some clinical settings in which a basal-bolus regimen is the preferred management choice, such as patients with type 1 diabetes or those with life-threatening, organ-threatening, or limb-threatening complications, as well as patients with late autoimmune diabetes of adults (LADA), brittle diabetes,

pancreatic diabetes, gestational diabetes, and new-onset diabetes after transplant (NODAT). Dietary habits and patterns affect glycemic diurnal variation and the number of prescribed daily insulin doses. Persons who follow a very high carbohydrate diet will respond better to high-mix insulins, while patients at higher risk of hypoglycemia may opt for low-mix formulations.

Like all research studies, this investigation has certain limitations. Firstly, the study duration may not be sufficient to assess the long-term effects of thrice-daily insulin *versus* basal-bolus insulin. Secondly, the study population might not represent the entire spectrum of diabetes patients, which limits the universality and applicability of the results.

Conclusion

The use of thrice-daily premixed insulin is found to be non-inferior to the basal-bolus regimen when patients need to intensify their insulin therapy in terms of glycemic control and the frequency of hypoglycemic attacks. This approach offers the advantage of better patient convenience and compliance.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the scientific unit of Alkindy College of Medicine at its meeting numbered 25 and dated August 25th, 2023.

Consent to participate

Written informed consent was obtained from all the participants.

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