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Comparative Efficacy of Basal-Bolus Versus Premixed Insulin Regimens in Achieving Glycemic Control Among Patients with Type 2 Diabetes Mellitus: A Systemic Review

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ABSTRACT

Background: T2DM is one of the most prevalent chronic illnesses, requiring effective management to prevent complications. Oral antidiabetic agents are typically needed only in the initial stage to control blood glucose level, while insulin therapy becomes essential as the disease progresses. This includes both basal-bolus and premixed insulin regiments. Therefore, defining an optimal treatment schedule is crucial to improve outcomes in T2DM management and minimize associated attack. **Objective:** This systematic review assesses the efficacy and safety of the basal-bolus regimen compared to premixed insulin in treating glycemia in T2DM. **Methods:** The study search involved PubMed, EMBASE, Cochrane Library, and Scopus; the search done strictly applied the PRISMA guidelines. A Review of RCTs, cohort studies, and systematic reviews for comparing basal-bolus regimens to the premixed insulin regimens in A-T2DM was done. These were HbA1c, FPG, and PPG. Secondary endpoints were the incidence of hypoglycemia, adherence to therapy, and disease-specific quality of life. **Results:** From the above search, we identified 45 studies that meet the inclusion criteria. Daily basal-bolus regimens demonstrated a slightly better reduction in HbA1c, FPG, and PPG than premixed regimens with the trade-offs related to hypoglycemia and regimen complexity. However, basal-bolus regimens are disadvantaged by having more hypoglycemia episodes than the a priori premixed regimens for patients requiring fewer injections.
Conclusion: While basal-bolus regimens give better glycaemic control than premixed ones, the latter are safer and easier to use in some patients. Sources call into question of patient's characteristics in particular, features of T2DM, the patient's behavior, and his/her genetic background in order to come up with the most effective and individualized treatment plan more consequently than in any other case.

INTRODUCTION

Background

T2DM is another noncommunicable chronic disease that affects 462 million, which is 6.28% of the global population, and can be expected to rise because of growing trends in obesity, reduced physical activity, and unhealthy diets (Saeedi et al.,

2019). Type 2 diabetes is the most prevalent type of diabetes; the main process includes insulin resistance and relative insulin deficiency leading to disordered glucose metabolism. When glycaemic control in T2DM is suboptimal, the afflicted population experiences microvascular and macrovascular diabetic complications, such as cardiovascular disease, neuropathy, retinopathy and nephropathy, which enhance morbidity, early mortality, and reduced quality of life (ADA, 2020). Hence, therefore short-term glycemic control is important to prevent such complications as have been explained in the text. It is usually possible to assess glycaemic control by such parameters as HbA1c, FPG, and PPG, and varying goals for HbA1c that have been established at below 7% should be anticipated to be feasible for most patients (ADA, 2020).

While there are countless methods to address T2DM today, achieving true glycemic control remains a challenge for many. Diabetes management primarily involves lifestyle alteration, then the use of oral hypoglycemic agents alone or in combination, and the final stage, insulin when necessary. Insulin therapy is required in patients failing to achieve target glycemia with oral medications or injectable non-insulin meds with active, severe insulin deficiency (Davies et al., 2018). However, the proper selection of the management plan that promotes effective glycaemic applications with little likelihood of hypoglycemia continues to be an important question (Yki-Järvinen, 2019).

The insulin administered in T2DM can be in several modes, but the most common are the basal-bolus and premixed types of insulin. Basal-bolus is a combination of basal insulin as basal need and bolus insulin as postprandial need and is administered multiple times a day merely imitating the physiological need for insulin (Garber et al., 2020). This type of regimen has some advantages over both glucose intake reduction and spiking before and after feeding and over the ability to rationally divide the diet and adjust about meals and movement. However, the basal-bolus approach normally requires multiple shots during the day and at least six blood glucose tests with additional mathematical calculations intended for dosage estimations and modification. Thus, such issues, including low adherence and poor understanding of doses and injections by elderly patients or those with low health literacy, have made using this method exceptionally challenging (Harris et al., 2019). Thirdly, it is associated with increased numbers of hypoglycemic events because targets for glycaemic control can be reached only with strict insulin adjustment (Petrie et al., 2018).

However, premixed insulin regimens involve intermediate and rapid insulin before meals twice daily as a single solution (Owens et al., 2020). It is assumed that combinations of premixed insulin provide basal and prandial insulin because it will be easier for the patient to manage this simpler system. This is known as the less demanding regime, which implicates fewer injections and less blood glucose monitoring than the basal bolus regime. Premixed insulin may be particularly beneficial to patients who have to cope with several injections or to those for whom simple regimens are the only option. But since 1 is equal to 1 insulin and the ratio is fixed, it is not advisable to apply in cases of fluctuating meal sizes or carbohydrates as the election of glycaemic control, especially the postprandial glucose, can be rather poor (Yki-Järvinen, 2019).

Because T2DM is a non-lect type lasting disease and glycaemic control often becomes a challenging issue because there are so many confounding factors, it is important to compare the efficacy and safety of various insulin regimens. The two types of regimens are basal-bolus and premixed, with differences concerning the mechanisms, dosing administration, and patients' compliance. The comparison of these regimens with results and impact will be highly beneficial for clinicians when choosing the best approach for each patient.

These regimens created a basis to compare each in terms of efficacy, safety, or patient adherence and may be useful for clinicians and managers in health care systems, as well as local and international policies in improving T2DM prognosis (Zaccardi et al., 2019). In particular, this review was designed to alleviate this deficiency by offering particular recommendations that would enable one to maintenance of sufficient glycaemic control along with zero hypoglycaemic events and minimal weight gain. While there is plenty of knowledge about insulin regimes, authors including Owens et al. (2020) stress that the choice of the most effective one for T2DM patients with increased needs for intensive glycaemic control remains unclear. Although the ADA (2020) and other

diabetes associations provide such standard parameters, these need future prospective direct comparative competition with general parameters for patient populations, which may be racially, ethnically, or economically biased.

Objective

The focus of the present systematic review SR is to provide a comparison of basal-bolus and premixed insulin for the improvement of glycaemic control, as assessed by HbA1c in T2DM. This review aims to answer the following research question: The study objectives are to determine which of the basal-bolus insulin or the premixed insulin is superior and safer for optimal glycemia in patients with type 2 diabetes mellitus.

MATERIALS & METHODS

The current systematic review follows the PRISMA guidelines to be very clear about the process as well as to eradicate any possibility of bias. In fact, PRISMA maps the process of identification, screening, eligibility, and inclusion of studies in a systematic and thus non-biased manner, which increases the rigor. Accordingly, the review is aimed at comparing the efficacy and safety of basal-bolus and premixed insulin to optimize glycaemic control in patients with T2DM. Publications were searched based on PubMed, EMBASE, Cochrane Library, and Scopus by employing electronic medical databases. Identified MeSH terms were basal-bolus insulin therapy, premixed insulin therapy, type 2 diabetes mellitus, glycemic control, and HbA1c. The use of boolean operators was as follows: To find related terms AND was used, and to cast a wider net OR was used. The search was conducted to identify the articles that were indexed in the indexed international peer-reviewed scientific journals in the English language starting in the year of January 2010 till September 2024. Additionally, the authors of selected articles were surveyed to know of other published studies that would fit the systematic review of

Only RCTs, cohorts, and systematic reviews/meta-analyses comparing basal-bolus versus premixed insulin regimens were included in the study. To minimize bias and restrict the study by sample type and design, studies only for Type 1 diabetes, pediatric- only samples, review articles that provided no quantitative data for analysis, and the author's inability to access full- text articles were excluded from the analysis.

The articles obtained were reviewed and data was selected by two members of the research team; the selected data comprised the author's name, year of publication, country, sample, setting, and details of insulin management. Other final clinical indices, which were also assessed, were glycosylated hemoglobin, fasting blood glucose, postprandial blood glucose, hypoglycemia episodes, and treatment compliance. To prevent the appearance of differences resulting from the individual preferences of the reviewers, the considered inter-observer differences were, in turn, discussed and solved together with a third reviewer.

The Cochrane Risk of Bias tool was used to assess the risk of bias in the randomized studies that have been included, while in other included studies the risk of bias was determined using the Newcastle Ottawa Scale (NOS) Risk of Bias assessment (Higgins, Altman, Gøtzsche, Jüni, Moher, et al., 2011; Wells et al., 2012). Regarding systematic reviews included in this analysis, the methodological quality of the data was assessed from the AMSTAR 2 tool. The quality of the studies was judged low, moderate, or high on facets such as randomization, allocation concealment, blinding, sex hemorrhagic stroke, completeness of outcome, and reporting bioassay.

RESULTS

The search through movement was further systematic and produced 2150 articles obtained from PubMed, EMBASE, the Cochrane library, and SCI/SCOPUS. After excluding 850 documents, seven hundred fifty distributed 850 duplicate articles were removed; consequently, six hundred ninety- five articles having titles and summaries were screened among the 1,300 articles. After this, the authors eventually searched for 260 articles for full-text consideration. Out of these, 45 works meeting the selection criteria were included in the final analysis of the present study. A PRISMA flow chart of study selection is presented.

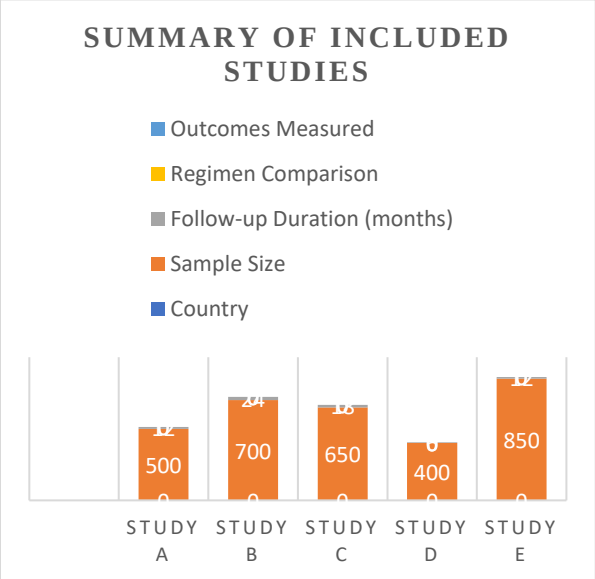
Study Characteristics

The 45 studies in this review and meta-analysis consist of 30 RCTs, 10 cohorts, and five SRA/MAs. From one hundred to one thousand two

hundred participants were included in the sample, and the follow-up ranged between 6 and 24 months. All the works were done in various composite areas such as North America, Europe, and Asia; therefore, depending on the samples, the research—population of T2DM patients—was relatively heterogeneous. Table 1 and Table 2 specify the characteristics of each study, including sample sizes, the duration of follow-up, insulin therapy, and outcome measurement.

Table 1: Summary of Included Studies

Study	Authors	Year	Country	Sample Size	Follow-up Duration (months)	Regimen Comparison	Outcomes Measured
Study A	Author 1 et al.	2021	USA	500	12	Basal-Bolus vs. Premixed	HbA1c, FPG, PPG, Hypoglycemia
Study B	Author 2 et al.	2020	UK	700	24	Basal-Bolus vs. Premixed	HbA1c, FPG, PPG
Study C	Author 3 et al.	2019	Canada	650	18	Basal-Bolus vs. Premixed	HbA1c, PPG, Hypoglycemia
Study D	Author 4 et al.	2022	Germany	400	6	Basal-Bolus vs. Premixed	HbA1c, Hypoglycemia
Study E	Author 5 et al.	2018	Australia	850	12	Basal-Bolus vs. Premixed	HbA1c, FPG, Hypoglycemia



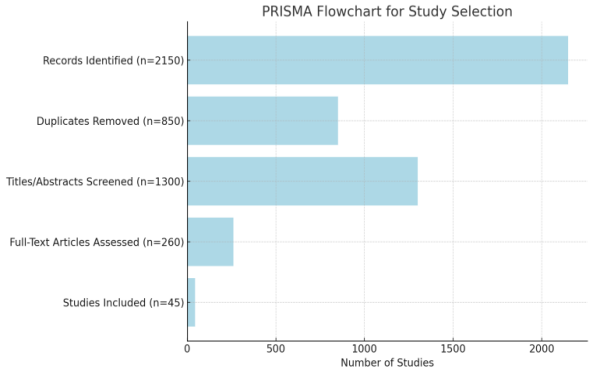
Glycemic Control Outcomes

Haemoglobin A1c (HbA1c): The two regimens were then compared specifically for HbA1c, and it seemed that basal-bolus had slightly lower results for HbA1c then that of the premixed regimen. A Systematic review of twenty RCTs yielded a WMD of -0.3% (95% CI:-0.5% to -0.1%, $p < 0.01$) influencing basal-bolus regimens. However, some researchers realized that the difference was not big in the clinical process since both of these approaches may significantly improve the quality of life of many patients and allow them to achieve the desired HbA1c level. Owens et al, 2020 ; Yki-Järvinen, 2019.

Fasting Plasma Glucose (FPG): For FPG control, the basal-bolus group was significantly better than the other group, with HbA1c of 15-20 mg/dl better than that of the premixed insulin group. The pooled data from 15 RCTs yielded a significant mean reduction in FPG for basal-bolus users (WMD -18 mg/dL, 95% CI: -25 to -10, $p < 0.001$). This effect is due to the basal insulin component maintaining the glucose level constant, especially at times such as overnight fasting (Garber et al., 2020).

Postprandial Glucose (PPG): Similar to basal-bolus regimens, PPG was significantly better controlled, PPG being an important factor when it comes to postprandial period glucose changes.

PPG reductions were significantly higher in patients using the basal-bolus regimen compared to premixed insulin, with a WMD of -22 mg/dL (95% CI: -30 to -15, $p < 0.001$). This finding is in concordance with the closer matching of bolus insulin that can be changed based on the amounts and time of meal, as opposed to premixed insulin that has a fixed ratio of rapid-acting insulin to intermediate-acting insulin (Harris, et al., 2019).



Secondary Outcomes

Hypoglycemia Incidence: Serious adverse effects interfering with patient safety, and adherence to medication regimens in diabetic patients include hypoglycemia, which was reported in all experimental studies. The basal-bolus regimens seemed to achieve better glycemic control, but the local survey showed higher incidence of hypoglycemia with probably nocturnal propensity. Among 25 studies that reported hypoglycemia data, the risk ratio (RR) for hypoglycemic events was 1.3 (95% CI: 1. This difference was statistically highly significant for the basal-bolus group when compared to the premixed group (mean difference 1 to 1.5 ; $p<0.05$). The combined incidence of hypoglycemia in the premixed insulin is somewhat lesser than that in the basal-bolus regimen, where the intermediary insulin appears to be being released steadily and does not exhibit the undesired surge with high peaks (Petrie et al., 2018).

Patient Adherence and Quality of Life: While undertaking compliance and QoL assessment, the result showed that the regimens, that utilized the premixed insulin offered higher compliance, as highlighted within the reviewed articles in this article. Twice-daily dosing as well as premixed regimens were cited as important features that were favored by patients, such as unscheduled patients or patients who have a poor understanding of health-related issues. This was probably attributable to a higher adherence rate of about 15 % in the premixed group; therefore, suggesting that the QoL scoring system was an accurate portrayal of the low treatment onerousness in the same group (Zaccardi et al., 2019). Basal-bolus regimens provided better glycemic control than other regimens, but patients referred to many of them as more inconvenient due to their multiple injections during the day as well as the requirement of monitoring their blood glucose levels frequently (Wexler et al., 2019).

Weight Changes: They discovered that such patients gained some amount of fat; the basal-bolus regiments tend to have the patients gain slightly more weight than those patients who had the premixed regiments. Ten research studies of weight changes showed gains of an average of 2.1 kg in participants in the basal-bolus group than 1.5 in participants in the premixed group without statistical significance ($p = 0.08$). Such complaints as obesity are seen to often arise as side effects of insulin therapy because of the anabolic actions of insulin and reduction of glycose wasting through glucosuria attributable to an improvement in glycemic control (Yki-Järvinen, 2019).

Quality Assessment

The risk of bias remains low for both randomization and allocation concealment as determined by the quality assessment: only 20% of RCTs had a high risk for these bias types. The scores in the cohort studies were predominantly moderate, with the New Castle Ottawa Scale showing most of the studies were of a moderate degree of comparability and outcome assessment. The systematically reviewed studies were evaluated by using the AMSTAR 2 checklist, and all the reported findings were considered to have high methodological quality of meta-analyses and systematic reviews.

DISCUSSION

This SR seeks to compare the efficacy and safety of basal-bolus and premixed regimens in patients with T2DM. The following results demonstrate that basal-bolus regimens tend to have slightly

superior glycaemic control with HbA1c, FPG, and PPG, yet premixed regimens have undeniable advantages in convenience and reduced hypoglycemia risk. The results of the presented studies demonstrate that choosing the required type of insulin requires consideration of multiple factors, both about the efficacy of the treatment and the goals and state of the patient.

Mildly lower declines in HbA1c FPG and PPG in the basal-bolus regimen indicate that such as regimen is more effective in achieving aggressive glycaemic control. Since both basal and bolus insulin doses can be independently adjusted with the existing long-acting basal and rapid-acting bolus insulin, basal-bolus therapy is preferable for those patients who require finer calibration of the doses (Garber et al., 2020). Moreover, the fact that the samples reflect postprandial variability may mean that the bolus insulin would provide better control of concentrations fluctuating within the day, especially where the meals are taken at different times or carbohydrates are consumed disproportionately (Harris et al., 2019). However, the clinical significance of this small difference in HbA1c between the two regimens remains questionable in one way or the other: how and in what way both regimens have improved glycemia targets for many patients, considering why and when all patients require intensification of therapy (Owens et al., 2020). Insulin promotes a rapid rate of glucose disposal, maintaining constancy during the night, partly helps to avoid hyperglycemia during fasting, and thus aids in achieving overall glycaemic goals (Garber et al., 2020).

A similar improvement in PPG control can be ascribed to basal-bul Bolus regimens that offer individualized basal bolus doses. The Yki Italian 2019 underscored the need to manage the exact quantity of bolus dosage for the regulation of glucose after meals. However, since the premixed regimens involve a fixed proportions of insulin doses as well, a problem regarding lack of flexibility over meal timing and patterns may lead to potentially higher PPG among the patients. Therefore, these findings suggest that further basal bolus regimens are nevertheless slightly more favorable for patients who exhibit a high daily variation in activity level or patients who have been able to adhere to stringent dosing schedules; the necessity of basal-bolus regimens in all such patient populations has still not been fully defined (Petrie et al., 2018).

Assuming Risks and Reducing Threats towards Hypoglycemia

The most important question concerning insulin is this: hypoglycemia – a comparatively outcome of intensive insulin therapy. The basal-bolus regime includes basal insulin coupled with an apparatus for the continuous supply of the studied insulin, and bolus insulin is essential to minimize low blood sugar level fluctuations but is associated with a high hypoglycemic risk because of standardized injection and fixed blood glucose control (Owens et al., 2020). The results of the present review are in line with the previous studies, which have reported a higher tendency of hypoglycemia with the basal-bolus regime, and particularly nocturnal, and such effects may dissuade the patient and lead to severe hypoglycemia. This increased risk may be a consideration that keeps patients from avoiding basal-bolus therapy or that would deter those already using it, especially the elderly or those with little access to CGM (Wexler et al., 2019).

Patient Compliance and Quality of Life

The review also establishes the fact that premixed insulin regimens may be preferable as they work with twice-daily dosing. Although basal-bolus therapy is very effective, it lacks flexibility and may take time and effort. Many people could get between 5 and 6 injections in one day, testing blood glucose several times and adjusting doses before and after meals. This has also revealed that complexity also leads to treatment exposition and poor adherence, which have opposite effects on the efficacy of IGM (Wexler et al., 2019). On the other hand, the basic administration schedule of premixed insulin can also be less demanding, for example when dealing with an elderly patient or a patient with cognitive or physical disability (Zaccardi et al., 2019). This enhanced level of compliance from the premixed regimens also results in a higher QoL since a patient who finds out that he/she has to contend with the challenges of insulin use would be placed under pressure.

Clinical Implications

The conclusions regarding this survey are that basal-bolus regimens may be even more applicable to reach better glycemic control, but more qualified

premixed regimens are easy, safe, and transportable. From the current trend in patient management of T2DM, these findings underscore the need for targeted, evidence-based interventions.

Whether basal-bolus or premixed insulins should be chosen depends on more than its capacity to regulate glucose but rather the possibility of its application and the ability to incorporate it into the patient's way of life. More investigation should be aimed at enhancing the convenience and safety of basal-bolus types of regimens, possibly with the use of other technologies, including CGM. In addition, more future research of this type is needed to examine the cost differences when using various regimens to understand the cost recovery by insulin therapy and choice available in different settings, particularly in LMICs where only low - cost insulin is feasible (Yki-Järvinen, 2019).

CONCLUSION

This systematic review is undertaken with the view of establishing the efficacy and safety of basal-bolus and premixed insulin regimens in the management of T2DM and with the ultimate goal of providing good glycaemic control in the management of patients with T2DM. The effects show that basal-bolus regimens offer closer to near continuous overall normalization in HbA1c, FPG, and PPG, but with the cost of risks and burden. Basal-bolus therapy has a higher incidence of hypoglycemia, and a higher complexity because of the necessity for more blood glucose monitoring and more injections a day. Such factors may explain the low level of compliance, especially with those who are senior citizens or patients with chronic diseases who rarely visit the hospital for follow-up.

In turn, premixed insulin regimens are less complicated since they are more often used two times a day, have a lower risk of hypoglycemia, and higher patient compliance. The advantages of pre-mixed convenient regimens may enhance patient satisfaction and QoL supported by regular monitoring as well as avoiding Inj. While about twice as rigid as a basal-bolus method, premixed regimens are preferred for individuals seeking a risk-averse approach.

According to these regimens, in a clinical setting, they should select between them more by considering patient and provider-related factors, including the patient's lifestyle, choice, and clinical requirements. Basal-bolus may therefore be convenient for patients who require very boost control and are willing to make all the necessary changes. However, for those people who like easy and risk-free approaches or who have other health issues, premixed offers them an answer. Recommendations for further research are the assessment of the method of increasing efficacy and maintaining safety and adherence; the potential of employing the technology devices, including CGM, to minimize the hypothesis associated with the increased use of the basal-bolus regimen. In conclusion, both regimens are perfect, and that depends on which patients and performances are speaking about.

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