Journal of Clinical and Nursing Research, 2024, Volume 8, Issue 6
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Research Progress on the Efficacy and Safety of Different Basal Insulins in the Treatment of Type 2 Diabetes Mellitus

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Abstract: *Objective:* To evaluate the efficacy and safety of different basal insulins in the treatment of type 2 diabetes mellitus (T2DM). *Methods:* The current research progress on different basal insulins was evaluated, with efficacy indicators including fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), and safety indicators focusing mainly on weight change and the incidence of hypoglycemia. *Results:* Several different basal insulins showed similar metabolic control effects in terms of fasting plasma glucose and glycated hemoglobin. However, the risk of hypoglycemia was lower with insulin glargine 300 (Glar-300), insulin degludec 100 (Deg-100), and insulin degludec 200 (Deg-200) compared to insulin glargine 100 (Glar-100). Additionally, Glar-300 had the least impact on weight. *Conclusion:* For the treatment of T2DM, different basal insulins have similar therapeutic effects, but there are differences in the incidence of hypoglycemic events and their impact on weight. Rational insulin selection and dosage adjustments should be made based on the different patient groups.

Keywords: Basal insulin; Type 2 diabetes mellitus; Hypoglycemia

Online publication: July 22, 2024

1. Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disease characterized mainly by chronic hyperglycemia. Its pathogenesis is primarily due to insulin secretion defects and/or insulin dysfunction. When the feedback loop between insulin function and insulin secretion becomes abnormal, it affects insulin functionality, leading to abnormally elevated blood glucose levels in patients [1]. According to the results of the China National HbA1c Surveillance System (CNHSS), less than one-third of T2DM patients achieve adequate HbA1c control [2]. Long-term abnormal blood glucose levels are closely related to various chronic complications, such as retinopathy and diabetic nephropathy. As the disease progresses, patients often experience β-cell failure, hyperglycemia, and hypoinsulinemia [3]. Ultimately, many patients still require intensive treatment, such as adding second-line oral antidiabetic drugs (OADs), non-insulin injectable therapies, or insulin treatment regimens on top of OAD therapy. However, the choice of insulin type during actual treatment is particularly important. This

article reviews available evidence from existing randomized controlled clinical trials (RCTs) to explore the safety and efficacy of different basal insulins in blood glucose control for T2DM patients, providing a more theoretical basis for the pharmacological management of T2DM.

2. Types and mechanisms of basal insulin

2.1. Types of basal insulin

Basal insulin (BI) can be mainly categorized into the following types [4]: neutral protamine Hagedorn insulin (NPH), insulin detemir (Detemir), insulin glargine 100 (Glar-100), insulin glargine 300 (Glar-300), insulin degludec 100 (Deg-100), insulin degludec 200 (Deg-200), and insulin icodec. Their corresponding pharmacokinetic (PK) and pharmacodynamic (PD) characteristics are as follows [5]: NPH reaches its peak in about 4–8 hours, can sustain action for 10–16 hours, has a half-life of 4 hours, with a dosing frequency of 1–2 times per day, and its steady-state time is not reported; insulin detemir has an onset time of about 4–7 hours, a smooth action curve with a duration of up to 24 hours, a half-life of 5–7 hours, a dosing frequency of 1–2 times per day, and reaches steady state in 1–2 days; Glar-100 has a smooth and peakless action curve, with a duration of up to 24 hours, a half-life of 12–14 hours, a dosing frequency of once daily, and reaches steady state in 2–3 days; Glar-300 has a smooth and peakless action curve, with a duration of up to 24–36 hours, a half-life of 23 hours, a dosing frequency of once daily, and reaches steady state in 4–5 days; Deg-100 has a smooth and peakless action curve, with a duration of less than 42 hours, a half-life of 25 hours, a dosing frequency of once daily, and reaches steady state in 4–5 days; Deg-200 has a smooth and peakless action curve, with a duration of less than 42 hours, a half-life of 25 hours, a dosing frequency of once daily, and reaches steady state in 4–5 days; for long-acting insulin preparations like insulin icodec, Phase 1 clinical trial results show that it can reach its peak in 16 hours, with a duration of 10–16 hours, a half-life of 196 hours, a dosing frequency of once weekly, and reaches steady state in 3–4 weeks.

2.2. Initiation timing and dosage of basal insulin therapy

For specific individuals, determining the exact time to initiate BI therapy can be challenging. It is generally considered appropriate to start basal insulin for those who have been on ≥ 1 OAD for more than 3 months without achieving target HbA1c levels; for T2DM patients with HbA1c > 9.0% or FPG > 11.1 mmol/L, with or without significant hyperglycemia symptoms, basal insulin combined with mealtime insulin can be selected to control hyperglycemia in a short period [6]. Regardless of the initial dosage, it is important to ensure strict and adequate insulin titration.

3. Head-to-head comparison studies of different basal insulins: efficacy and safety

3.1. Control of fasting plasma glucose and glycated hemoglobin

Fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) are two essential evaluation indicators for insulin efficacy in T2DM management. They help monitor patients' blood glucose control, facilitating the development and adjustment of treatment plans to prevent complications. A randomized controlled trial comparing Glar-100 and NPH showed that basal insulin analogs could provide a pharmacokinetic (PK) and pharmacodynamic (PD) profile closer to the normal physiological secretion pattern of insulin. This allows for a more even, predictable, and extended time-action profile for exogenous insulin supplementation, reducing the risk of hypoglycemia and making dosage regimens more flexible [7]. In another randomized controlled trial comparing Det and NPH, no significant difference in HbA1c regulation levels was found between Det and NPH. The average

change in HbA1c for NPH ranged from -1.9% to -0.32%, while for Det, it ranged from 0.02% to 0.28%, showing no significant difference in the comparison results [8]. As one of the most comprehensively studied weekly insulin preparations globally, Phase II clinical research results for insulin icodec have been published. Icodec insulin has been shown to reduce the risk of hypoglycemia and allow flexibility in dosage regimens [9]. Therefore, whether in insulin initiation or conversion therapy for T2DM patients, insulin icodec can achieve once-weekly injection with both efficacy and safety.

3.2. Impact on weight

Different basal insulins have varying impacts on weight, and weight management is an important aspect of diabetes treatment. Therefore, it is necessary to balance blood glucose control and weight management when choosing a treatment plan. In studies comparing Deg and Glar-100, no significant differences in weight gain were found between the two; however, trials comparing Glar-300 and Glar-100 found that patients treated with Glar-300 had significantly less weight change, with some studies even reporting significant weight loss in patients treated with Glar-300. Regarding insulin dosage, research results also showed that patients treated with Deg required a lower total daily insulin dose than those treated with Glar-100. At the end of the study, patients in the Glar-300 treatment group required a higher insulin dose compared to the Glar-100 treatment group [9]. In trials comparing Glar-300 and Deg-100, the least squares mean difference in weight change for Glar-300 compared to Deg-100 was -0.33 kg (95% CI: -0.81 to 0.15). Regarding total daily insulin dose, the average doses from baseline to week 24 increased by 33.6 ± 24.4 U (0.36 ± 0.25 U/kg) and 29.1 ± 23.3 U (0.31 ± 0.24 U/kg) for the Glar-300 and Deg-100 groups, respectively [10]. In a randomized controlled trial comparing Deg-200 and Glar-300, the weight change at the end of the treatment was greater in the Deg-200 group than in the Glar-300 group (2.9 ± 5.2 kg vs. 1.7 ± 5.8 kg), with an estimated treatment difference of 1.18 kg (95% CI: 0.60 to 1.75). Regarding insulin dosage, the insulin doses at the end of the treatment for the Deg-200 and Glar-300 groups were 66.6 ± 48.5 U and 73.0 ± 48.5 U, respectively [11]. Therefore, to achieve blood glucose control goals, the total daily insulin doses for Glar-300 and Deg-100 need to be increased.

3.3. Incidence of hypoglycemic events

In T2DM patients undergoing basal insulin therapy, failing to appropriately adjust the dosage or choose the correct insulin type can increase the risk of hypoglycemia. Different types of basal insulins have different pharmacokinetic characteristics, thereby affecting the risk of hypoglycemia differently. Studies have indicated that the incidence of confirmed and nocturnal hypoglycemia in patients treated with Glar-100 is lower compared to NPH. A study on the Gulf population showed that even for patients with inadequate or ineffective blood glucose control with oral antidiabetic drugs, Glar-300 still provided good blood glucose control throughout the dosage adjustment cycle without any hypoglycemic events [12].

4. Dosage adjustment and medication

In clinical practice, special populations among T2DM patients also require special attention, particularly elderly patients with multiple comorbidities and those with renal insufficiency. Due to the risk of hypoglycemia and limited operational ability, these patients need antidiabetic medications that are easy to use, with a low risk of hypoglycemia and minimal blood glucose fluctuations. At this time, the flexibility and variety of dosage adjustments for new basal insulins can meet the clinical medication needs of such patients. In clinical trials involving Glar-300 insulin, patients using the new basal insulin treatment required only a once-weekly dosage adjustment regimen to achieve good blood glucose control [12]. The characteristics of basal insulin are highly beneficial for

patients in coping with various daily life changes, but it is still recommended that patients follow medical advice and take it at a fixed time every day to achieve long-term reasonable blood glucose control.

5. Conclusion

In T2DM patients, β-cell function is generally impaired. When the damage accumulates to a certain extent, even with the addition of OADs, endogenous insulin is insufficient to control blood glucose. At this time, patients often need to supplement with exogenous insulin, but the appropriate timing for supplementing exogenous insulin in clinical practice is often difficult to determine. Studies have confirmed that more than half of newly diagnosed T2DM patients require insulin treatment after six years of OAD therapy [13]. Especially for symptomatic patients with persistent hyperglycemia, weight loss, and a tendency toward ketosis, timely and effective insulin therapy is necessary. However, due to a lack of understanding of basal insulin, fear of injections, the complexity of insulin use and dose adjustment based on self-monitoring, and fear of hypoglycemia [14], clinical insulin therapy is often delayed. Some studies have even reported that in T2DM patients with HbA1c > 7%, the delay in insulin therapy can be as long as seven years or more [15]. Therefore, timely and appropriate use of BIs to treat T2DM is particularly important. With the emergence of basal insulin and its analogs, these drugs have been proven to have similar metabolic control effects in T2DM patients, but there are still certain differences in weight, incidence of hypoglycemia, and insulin dosage [16].

This article reviews and evaluates existing research evidence, and the results show that for blood glucose control in T2DM patients, choosing Glar-300 and Deg-100 compared to Glar-100 provides the same metabolic control effect with a lower risk of hypoglycemia. Comparative studies between Glar-300 and Deg-100 indicate that Glar-300 has a lower risk of hypoglycemia. The emergence of new weekly insulin preparations can improve patient adherence and has broad application prospects. In the future, the role of insulin in the field of T2DM treatment research will remain irreplaceable. With the development of oral preparations, weekly insulin preparations, and combination preparations, its prospects are promising, but the efficacy and safety of basal insulin still require continuous attention. Only through reasonable clinical selection and application can the best therapeutic effect be achieved.

Funding

Health Research Project of the Kunming Municipal Health Commission (Project No. 2022-03-06-015)

Disclosure statement

The authors declare no conflict of interest.

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