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Overview of differences between analogue insulin and human insulin in the management of diabetes: Efficacy, limitation, and cost

Tổng quan sự khác nhau giữa analog insulin và human insulin trong điều trị đái tháo đường: Hiệu quả, hạn chế và chi phí

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Abstract

Insulin therapy is the primary therapy in the treatment of Type 1 Diabetes (T1D) patients. And is an additional therapy for patients with Type 2 Diabetes (T2D), which is combined with Non-insulin drugs in order to be more effective in treatment [4]. Choosing the right type of insulin for each patient plays an important role in ensuring that the treatment is highly effective, minimizing the side effects caused by the drug and bringing many economic benefits to the patients. In order to compare the differences between two types of insulin currently available on the market, analogue insulin and human insulin in the treatment of T1D and T2D, this study used literature review method to collect and analysis information from documents, books, papers, researches conducted and published scientifically from 2010 to now with content related to Diabetes mellitus (DM) and insulin preparations. **Results:** For T1D patients, rapid-acting insulin analogues (RAIAs) were more effective in glycemic control and less hypoglycemic compared to regular insulin human (RHI). The prevalence of hypoglycemia in T1D patients, who are treated with basal insulin analogue, is relatively lower than medium-acting insulin (Neutral Protamine Hagedorn - NPH). In patients with T2D, the combination of basal analogue insulin with oral agents increases the likelihood of achieving target blood glucose (HbA1C $\leq$ 7%) and reduces the rate of hypoglycemia higher than NPH insulin [5]. Despite the cost of treatment is higher than human insulin, but analogue insulins are still recommended for treatment in T1D patients because of the effects and benefits it provides. For some patients who have difficulty in the cost of treatment, the use of human insulin or mixed insulins also helps the patient to achieve the glycemic goal.

Keyword: Diabetes mellitus; Insulin; Efficacy; Cost; Limitation.

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Tóm tắt

Sử dụng insulin là liệu pháp chính trong điều trị đối với các bệnh nhân Đái tháo đường (ĐTĐ) typ 1. Và là liệu pháp bổ sung đối với bệnh nhân ĐTĐ typ 2, được kết hợp với các thuốc Non - insulin nhằm mang lại hiệu quả cao hơn trong điều trị [4]. Lựa chọn đúng loại insulin cho từng đối tượng bệnh nhân đóng vai trò quan trọng để đảm bảo việc điều trị đạt được hiệu quả cao, giảm thiểu những tác dụng không mong muốn do thuốc và góp phần mang lại nhiều lợi ích về kinh tế cho bệnh nhân. Với mục tiêu so sánh sự khác nhau giữa hai loại insulin đang có mặt trên thị trường hiện nay là insulin analog và insulin human trong điều trị ĐTĐ typ 1 và ĐTĐ typ 2, nghiên cứu này sử dụng phương pháp tổng quan tài liệu để phân tích thông tin từ các tài liệu, sách, báo, nghiên cứu được thực hiện và công bố khoa học từ năm 2010 đến nay có nội dung liên quan đến bệnh ĐTĐ và các chế phẩm insulin. Kết quả: Đối với các bệnh nhân ĐTĐ typ 1, các insulin có tác dụng nhanh ngắn của analog (chất tương tự insulin người) mang lại hiệu quả cao hơn trong việc kiểm soát đường huyết và ít gây hạ đường huyết hơn khi so sánh với insulin human (regular). Tỷ lệ hạ đường huyết ở những bệnh nhân ĐTĐ typ 1 điều trị bằng insulin nền analog tương đối thấp hơn so với insulin có tác dụng trung bình (Neutral Protamine Hagedorn - NPH). Ở bệnh nhân ĐTĐ typ 2, việc kết hợp insulin nền analog với các thuốc đường uống làm tăng khả năng đạt được đường huyết mục tiêu (HbA1C ≤ 7 %) và giảm tỷ lệ hạ đường huyết cao hơn so với insulin NPH [5]. Mặc dù chi phí điều trị cao hơn so với insulin human nhưng insulin analog vẫn được khuyên dùng trong điều trị ở bệnh nhân ĐTĐ typ 1 vì những hiệu quả và lợi ích mà nó mang lại. Đối với một số bệnh nhân gặp khó khăn về chi phí điều trị bệnh thì sử dụng insulin human hoặc các insulin hỗn hợp cũng giúp cho bệnh nhân đạt được mục tiêu đường huyết mục tiêu.

Từ khóa: Đái tháo đường; Insulin; Hiệu quả; Chi phí; Hạn chế.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by increased hepatic glucose production and reduced glucose use in muscle and adipose tissue leading to abnormal glucose accumulation in the blood [3], [6]. According to the report of the International Diabetes Federation (IDF) in 2021, there are about 537 million adults with DM in the world, the statistics have shown that this rate will increase and is expected to increase to 643 million people by 2030 and 783 million people by 2045 [7]. In Vietnam, Diabetes is a burden of disease, according to IDF statistics in 2019, there are nearly 3.8 million people between the ages of 20 and 79 with DM and in the future this number may rise to 6.3 million by 2045 [8].

Administration of exogenous insulin sources is the primary and essential treatment for glycemic management in patients with T1D and T2D [2], [6]. The discovery of insulin represented a milestone in clinical medicine, it has saved the lives of millions DM patient in worldwide [9]. Only one year after treatment, insulin contributed to the reduction of mortality of diabetes ketoacidosis from 90% to 60% and to only 3% - 10% in 1974 [10]. Insulin is a hormone that is synthesized from β cell in the pancreatic islet of Langerhans [14]. The structure of insulin consists of two chains of polypeptide, chain A with 21 amino acids and chain B with 30 amino acids, in chain A there is a disulfur bond, between chains A and B there are two disulfur bonds (Figure 3.1) [3], [14]. In our body, insulin plays an important role in carbohydrate metabolism, energy storage, when excess carbohydrates will be stored as glycogen primarily in the liver and muscles or converted to fat stored in adipose tissue [14].

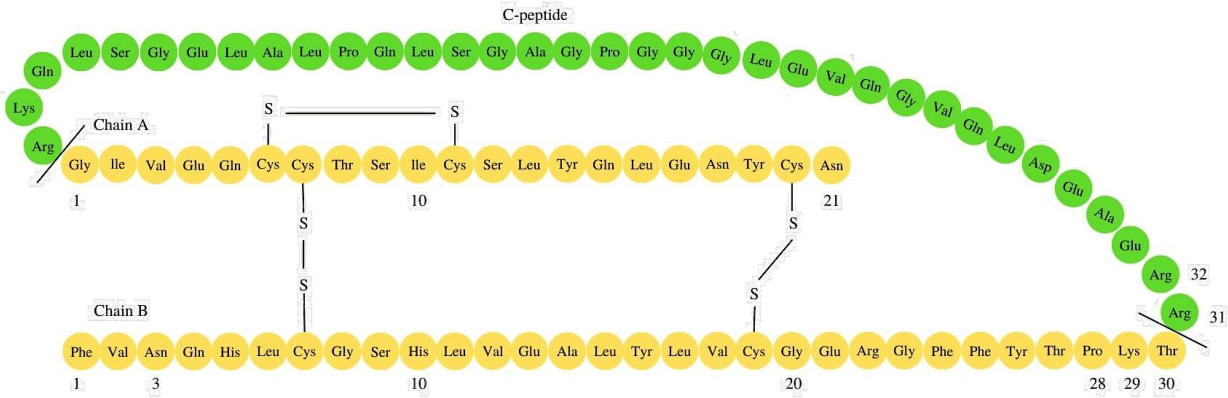

Figure 1.1. Structure of insulin [3], [14]

Over the last 100 years, many insulin studies have been conducted and new generation of insulin has been born (Figure 3.2), thanks to the outstanding improvements that not only have been highly effective in treating diabetes but also have positive impacts on the quality of life of patients [11], [12]. Insulin was first administered to humans in 1922, when a 14 years old patient with T1D in critical period had positive responses after injection of pure insulin extracted from the pancreas of calves is studied by scientist James B. Collip [9]. By 1946, the advent of NPH insulin, as the first medium-acting insulin, could help patients reduce the number of injection in a day (requiring only one or two injections per day) [15]. Then, in 1982, human insulin was born as a result of the recombinant DNA technology that replaced earlier animal-derived insulin types [16]. From the 1990s to present, the advent of analogue insulins has been a new step forward. By changing some amino acids in the structure of human insulin that have produced different types of insulin whose physiological function is almost identical to human insulin [17]. The first analogue insulin was introduced in 1996 called lispro, which is a rapid-acting insulin, is used in a way that intensifies with the meal so that patients can control their postprandial glucose, aspart was approved and released in 2000, while glulisine in 2004 [18-20]. In 2000, the invention of glargine, the first long-acting insulin, ushered in a new era in the treatment of diabetes with insulin, which could help patients reduce the time of using insulin and improve their quality of life [21], [23]. Beside glargine insulin, new generation analogue insulins such as determir insulin and degludec insulin were also approved as basal insulin which were born in 2005 and 2013 [12], [22]. Nowadays, in addition to rapid-acting or long-acting insulins, mixed insulins such as 70% NPH, 30% regular; 30% aspart protamine, 70% aspart; 50% lispro protamine, 50% lispro, are also found to be a convenient therapy that contributes to help patients control their disease better and provides more benefits in terms of treatment costs than some other types of insulin.

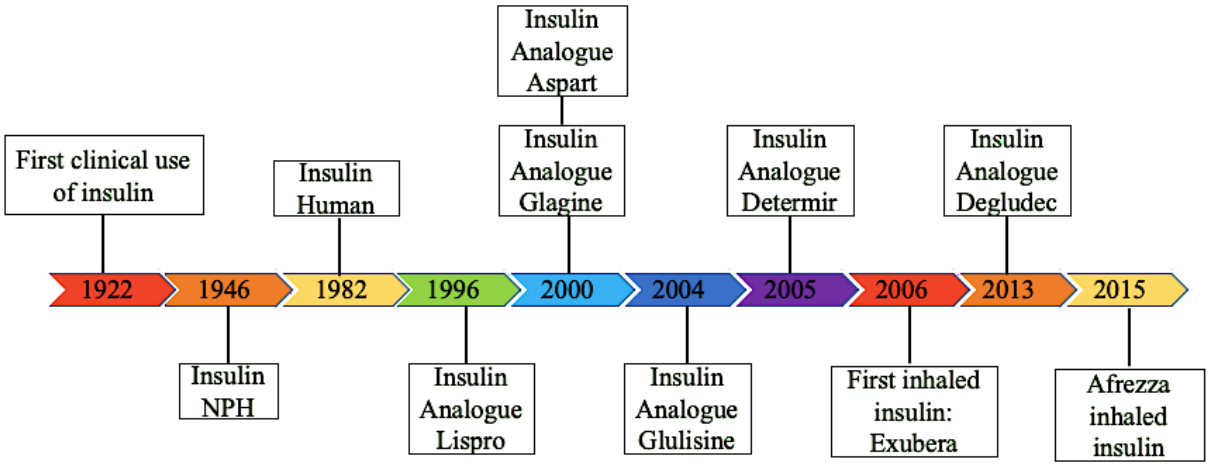

Figure 1.2. History of insulin [3], [24]

Analogue insulins were created to overcome the short-coming of human insulin in treatment of DM [13]. Basal insulin analogues have an effectivess duration (18 - 42 hours) (Table 4.1). Therefore, analogue insulin cause less variability, less hypoglycemia and less weight gain than human insulin (NPH insulin). RAIAs were developed to speed up insulin absorption relative to human soluble insulin, and thereby more effectively minimize postprandial glucose excursions and reduce the risk of hypoglycemia due to exogenous insulin concentrations remaining high for longer than needed [55]. On the other hand, many patients still consider in choosing between analogue insulin and human insulin because the cost of analogue insulin is higher than human insulin. Therefore, it is essential to overview the differences between these two types of insulin in terms of efficacy, limitation as well as treatment costs, that helps the pharmacist and patients to get the necessary information to be able to choose the type of insulin for more effective and optimal DM treatment.

Table 1.1. Classification of insulin [1], [3], [6]

Preparation	Brand name	Onset (hours)	Peak (hours)	Effective duration (hours)	Treatment subject	Route of Administration
Short-acting human insulin						
Regular insulin	Actrapid Insunova-R	0,5 - 1	2 - 3	6 - 10	T1D, T2D	SC, IM, IV
Rapid-acting insulin analogue						
Lispro insulin	Humalog Admelog	0,25 - 0,5	0,5 - 1,5	3 - 6,5		
Aspart insulin	NovoLog NovoRapid	0,17 - 0,33		3 - 5		
Glulisine insulin	Apodre	0,25 - 0,5		4 - 5,3		
Medium-acting insulin human						
NPH Insulin	Humulin-N Novolin-N	1 - 2	6 - 14	10 - 16	T1D, T2D	SC, IM, IV
Long-acting insulin analogues						
Glargine insulin	Lantus	1,1	0	24	T1D, T2D	SC, IM, IV

Determir insulin	Levemir	1,1 - 2		12 - 24		
Degludec insulin	Tresiba	1 - 4		24 - 42		
Mixed human insulin						
Mixed human insulin	Humulin 70/30	0,5 - 1	1,5 - 12	7,5 - 24	Most for T2D	SC, IM
	Mixtad 30/70					
	Mixtad 50/50					
Mixed analogue insulin						
Mixed insulin lispro	Humalog Mix 50/50	< 0,25	1 - 4	> 22	Most for T2D	SC, IM

2. Research subject and methods

This article used the literature review method to collect and analysis the information from books, articles, scientific reports, research topics are conducted and published scientifically from 2010 to now with content related to DM and insulin preparations to overview of differences between the two types of analogue insulin and human insulin, thus providing recommendations for the selection and use of insulin treatment for patients with T1D as well as T2D.

3. Result

3.1. Efficacy

The purpose of using bolus insulin is to help patients control prosprandial glycaemic, because approximately 50% of the total hyperglycemia episodes in patients on multiple doses of insulin is contributed by postprandial glucose fluctuation [25]. Faster onset of action of RAIAs has improved postprandial glycaemic control in DM patients (Table 4.1) [54]. In 2020, a meta-analysis by Antonio Nicolucci et al. have shown that the use of RAIAs significantly reduced posprandial glucose compared with the use of RHI in patients with T1D and the HbA1C levels were also lower in patients who used RAIAs than RHI [26]. In 2011, a study in German by Lutz Heinemann found that patients who used lispro insulin had lower postprandial glucose levels in three hours post-injection than regular insulin [27]. Nowadays, there are not many studies demonstrated the glycemic control effect in T2D of RAIAs compared to RHI. Another study in 2020 have shown that the effectiveness of treatment and control of HbA1C levels in patients with T2D in both types of insulin was the same after surveying 3 groups: the group of patients using analogue insulins, the group of patients using regular insulin and the group of patients using mixed insulin (analogue + regular) [28]. In contrast, a randomized trial of 13 patients with T2D used aspart insulin or regular insulin showed that postprandial glucose after eating two consecutive meals in patients who received insulin aspart decreases more sharply than regular insulin [29].

To provide high therapeutic efficacy, bolus insulins are often indicated in combination with basal insulins in treatment regimens. In some studies, compared long-acting insulin analogues (LAIAs) such as glargine or detemir with NPH insulin, the glycemic control between this two insulin was similar in both T1D and T2D patients. However, treatment by glargine insulin significantly reduced the variability of fasting plasma glucose (6.6 mmol/L) in T1D patients [32], [33]. In 2013, a study in Canada showed that glycemic control of LAIAs was superior to regular insulin, they found that

glargine once daily, detemir once daily or detemir twice daily significantly reduced hemoglobin A_{1c} compared with NPH once daily [34]. According to the study assessment of the effect of preparation insulins in the treatment of patients with T1D, although, the use of LAIAs in place of NPH insulin does not increase the proportion of patients who attained optimal glycemic control nor severe hypoglycemic complications were not completely eliminated, but, the authors has also found that with the possibility of reducing from 0.3% to 0.4% of HbA1C and the relatively low rate of hypoglycemia in patients gives the LAIAs many clinical interests [35]. A study in Netherlands in 2015 showed that the combination of glargine insulin with oral hypoglycemic drugs increased the likelihood of achieving a glycemic target of HbA1C ≤ 7% (53mmol/mol) in patients with T2D higher than NPH insulin [36]. Nonobese patients should use glargine insulin because it can reduce the HbA1C more than NPH insulin [37].

Mixed insulin regimen is an optimal option in patients with T2D at the onset of insulin therapy [39]. Mixed insulins are ready-mixed between two types of rapid-acting and long-acting insulins. In 2016, a research in Iran showed that in the group of T2D patients, who received mixed insulin aspart 30 (BIAsp 30 - Biphasic Insulin aspart 30) after 48 weeks had the rate of achieving glycemic goals delineated by the ADA (HbA1C ≤ 7%) higher than the group of patients in the combination of NPH + regular (NPH/Reg) (65% > 33%) but the glycemic control between these two groups was similar when the group of patients in BIAsp 30 had HbA1C reduction of 2.40 ± 1.28°% after 48 weeks and the group of patients in NPH/Reg had HbA1C reduction of 2.34 ± 1.53°% [5], [40]. The combination of neutral protamine lispro + insulin lispro (75/25 and 50/50) has a faster glycemic reduction than the combination of 70% NPH + 30% regular insulin, the postprandial glucose of these patients is lower as well as there is no significant variation of glucose concentration in the midday or overnight and it is usually administered 15 minutes before or immediately after a meal [41]. In several survey studies in patients with T2D switched from mixed human insulin (Biphasic Human Insulin 30 - BHI 30) to mixed analogue insulins (Biphasic Insulin aspart 30 - BIAsp 30) showed a marked improvement of HbA1C, fasting plasma glucose and postprandial plasma glucose improved significantly after 24 weeks and quality of life was positively impacted [42], [43].

3.2. Limitation

The advantage of being able to exert a shorter effect, the RAIAs reduces the risk of hypoglycemia in TD patients when compared to RHI. According to American Diabetes Association 2022 (ADA 2022), in T1D patients were treated by analogue insulins have lower rates of hypoglycemia and weight gain compared to regular insulin [6]. RAIAs can reduce 7% in total hypoglycemic episodes, 32% in severe hypoglycemia and 45% in nocturnal hypoglycemia levels in patients with T1D, this is an important finding, as these episodes are particularly associated with lower quality of life and treatment nonadherence [25]. In patients treated with regular insulin, there is a higher incidence of hypoglycemia than patients treated with analogue insulins (lispro or glulisine) due to the quick onset of action and shorter duration of action compared to regular insulin, so analogue insulin can helps patients reduce the risk of hypoglycemia, especially nocturnal hypoglycemia more than regular insulin [31]. In addition to insulin aspart reduces lipolysis more effectively than regular insulin, reduces levels of free fatty acids and proinsulin in T2D

patients [29]. Increasing levels of free fatty acids in the plasma due to lipolysis have detrimental effects on cell function and insulin sensitivity [52]. the effectiveness of treatment for the acute complications such as diabetes ketoacidosis (DKA) is also an important factor of insulin preparations, in a survey on the effectiveness of treatment for DKA patients found that analogue insulins is equally effective and safe as regular insulin in the treatment of DKA and there was not much difference observed in the patients's length of hospitalization in either group [30].

The adverse effects such as weight gain or hypoglycemia are reported to be less frequent in T1D patients who are treated by LAIAs compared to NPH insulin [34]. Some clinical trials have shown that long-term treatment with analogue insulins reduces the risk of hypoglycemia, especially nocturnal hypoglycemia compared to NPH insulin [32], [33]. A study in Poland 2011 shown that treatment with insulin determir was associated with a significant reduction in all hypoglycemic episodes and less weight gain in comparison with NPH insulin, moreover, they also found statistically significant benefits of insulin determir over NPH insulin in terms of noctural hypoglycemia [53]. In 2022, a study in Canada by Vanessa C Brunetti et al. found that the risk of cardiovascular events of the patients with T2D, who used LAIAs, is lower than NPH insulin and NPH insulin causes weight gain 4.5 times more than glargine insulin [38].

In long-term treatment, the combination of detemir insulin + aspart insulin was superior to NPH insulin + aspart insulin in less causing hypoglycemia [38]. In patients with T2D are treated by mixed analogue insulin, there is less frequency of minor, major and nocturnal hypoglycaemic compared to those using mixed human insulin [40]. In patients with T2D switched from BHI 30 to mixed analogue insulin BIAsp 30 showed the proportion of patients reporting hypoglycaemia decreased significantly, was from 2.18 events/patient-year to 0.06 events/patient-year and no nocturnal or major hypoglycaemic events were reported [43]. In addition, less weight gain (+ 0.22 ± 1.55) is one of the advantages of mixed analogue insulin when compared with mixed human insulin (+ 2.10 ± 2.69) [40], [42].

3.3. Costs

The cost of treatment plays an important part of effective disease control and is also received much attention from patients. Over the years, the payments for insulin have increased rapidly and outstripped other medical expenses, the insulin prices have tripled between 2002 - 2013 [44]. In the United States, the cost of analogue insulins is significantly higher than human insulin, estimated for each patient have to pay about $507.89 for analogue insulin and $228.20 for human insulin in 2013 [45]. Also in the United States, according to the statistics on GoodRx Health in 2019 has shown that diabetes patients have to pay a range of $27 to $99.4 per 10 ml vial of human insulin while the price of analogue insulin ranged from $248 to $600 [46]. Although analogue insulins are more flexible and can help patients improve their quality of life better than human insulin, but the reality is that many patients cannot afford to use it because the cost is higher than their income [47]. In US, a study in 2019 found that human insulin helps patients to save more economically, leading to better adherence and treatment efficiency [48].

High out-of-pocket costs for insulin can lead to cost-related nonadherence and poor outcome in patients with diabetes [49]. Patients may arbitrarily quit or reduce the dose of insulin to reduce the cost of insulin therapy [7]. A survey in the United States has shown that one out of

four patients is unable to control their blood glucose steadily due to the cost of medication [50]. Nonadherence to treatment leads to poor glycemic control and increases the risk of serious complications. While the disparity in prices may not be the most important issue in high-income countries, but it has a huge impact on low and middle-income countries.

4. Discussion

In terms of therapeutic efficacy, RAIAs have pharmacological action profile mimic the normal physiological insulin secretion in response to meals better than RHI, so RAIAs can offer a clear benefit in improving postprandial glucose in patients with T1D. Beside that glycemic control of LAIAs in T1D patients was more superior than NPH insulin, LAIAs significantly reduced the fasting plasma glucose (6,6mmol/L). In the treatment of T2D, the use of analogue insulin and human insulin showed similar glycemic control, while RAIAs offer no advantage for glucose control or reduce limitations, LAIAs combined with oral agents has the potential to help T2D patients achive a glycemic target of HbA1C $\leq$ 7% higher than NPH. In addition, mixed insulins are also more commonly indicated in patients with T2D than in patients with T1D because of the high efficacy it provides as well as saving the cost of treatment for patients because the cost of mixed insulins is lower than other types of insulin.

The hypoglycemia, especially nocturnal hypoglycemia in these patients are also markedly improved on switching from human insulin to analogue insulin. According to the ADA 2022, it is recommended that in most patients with T1D, RAIAs should be used to reduce the risk of hypoglycemic complications and ketosis complications [6]. Moreover, the combination regimens of basal insulin analogue with an oral drug or bolus insulin analogue significantly reduced the proportion of patients with hypoglycemia, especially nocturnal hypoglycemia. Although the cost of analogue insulins (glargine, lispro) is higher than human insulins (NPH, regular), but they do not significantly increase glycemic improvement, nor minimize the risk of hypoglycemia in patients with T2D [51]. Therefore, human insulin may be a suitable option for patients with T2D.

Although the cost of analogue insulins is significantly higher than human insulin, but it is still recommended for patients with T1D because of its high flexibility. Analogue insulin can provide an immediate action, so it is not only highly effective for glycemic control but also helps patients improve their quality of life and provide more therapeutic satisfaction than human insulin. However, the high cost is also a limitaion because it can lead to the nonadherence. Human insulin or mixed insulin is an appropriate choice for DM patients, that can helps patients have a better adherence, achive a glycemic goal and especially save more economically.

Choosing and prescribing an insulin preparation can be based on a variety of factors: the state of the disease, risk factors, complications or background disease and also the cost of treatment appropriate to the individual patient 's ability to pay. The goal of insulin therapy for patients with T1D and T2D is to achieve the therapeutic goal with a low rate of hypoglycemia and minimal weight gain, so in the treatment of diabetes it is necessary to personalize the therapeutic goal in each patient, in addition to having to balance the ability to control blood glucose and the risk of hypoglycemia to provide the most appropriate and optimal treatment regimen to achieve high effectiveness in treatment, especially good glycemic control for patients.

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