Insulin Therapy in Type 2 Diabetes: Insights into Clinical Efficacy, Patient-reported outcomes, and Adherence Challenges

Emad-Eldin et al., Insulin Therapy in Type 2 Diabetes: Clinical Insights and Adherence Challenges

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Abstract

Insulin therapy plays a crucial role in the management of type 2 diabetes as the disease progresses. Over the past century, insulin formulations have undergone significant modifications and bioengineering, resulting in a diverse range of available insulin products. These products exhibit distinct pharmacokinetic and pharmacodynamic profiles. Consequently, various insulin regimens have emerged for the management of type 2 diabetes, including premixed formulations and combinations of basal and bolus insulins. The utilization of different insulin regimens yields disparate clinical outcomes, adverse events, and, notably, patient-reported outcomes. Patient-reported outcomes offer valuable insights from the patient's perspective, serving as a valuable mine of information for enhancing healthcare and informing clinical decisions. Adherence to insulin therapy, a critical patient-reported outcome, significantly influences clinical outcomes and is influenced by multiple factors. This review offers insights into the clinical effectiveness of various insulin preparations, patient-reported outcomes, and factors impacting insulin therapy adherence, aiming to enhance healthcare practices and inform clinical decisions for individuals with type 2 diabetes.
**Key Words:** Insulin; Diabetes; Patient-reported outcomes; Pharmacokinetic; Pharmacodynamic; Adherence.

Emad-Eldin M, Balata GF, Elshorbagy EA, Hamed MS, Attia MS. Insulin Therapy in Type 2 Diabetes: Insights into Clinical Efficacy, Patient-reported outcomes, and Adherence Challenges. *World J Diabetes* 2024; In press

**Core Tip:** Understanding the dynamics of insulin therapy in type 2 diabetes is crucial for managing the disease effectively. This review navigates through the evolution of insulin formulations, emphasizing the impact of different regimens on patient-reported outcomes. Adherence to insulin therapy, a pivotal factor for successful outcomes, is explored alongside various insulin preparations and the influencing factors. Gaining insight into these dynamics can steer healthcare strategies, ultimately refining decision-making and boosting patient outcomes in the management of type 2 diabetes.

**INTRODUCTION**

Diabetes mellitus (DM) is a non-communicable disease that has become increasingly prevalent worldwide. DM affects all patient's age categories from children to elders. According to the 10th edition of the international diabetes federation Atlas of Diabetes, the worldwide estimation of diabetes is about 536.6 million people (representing 10.5% of the total population) which means more than 1 in 10 adult persons suffer from this disease (1). Type 2 diabetes mellitus (T2DM), constituting over 90% of global diabetes cases, exhibits a persistent and rapid escalation in both prevalence and the consequential burden experienced at both individual and health system levels (2).

DM is a disease described by the disturbance of glucose hemostasis owing to the malfunction of insulin in the target tissues causing abnormalities in the fats, protein, and carbohydrate metabolism. The principal hallmark of the disease is elevated glucose
in the venous plasma which is the gold standard for the diagnosis of DM (3). The elevation of plasma glucose is caused by absolute insulin deficiency as in type 1 diabetes (T1DM) or increased insulin resistance as in T2DM or both (4). Consequently, prolonged insulin deficiency or resistance give rise to a spectrum of metabolic dysfunctions, precipitating insidious complications (5). Insufficient or neglected management of hyperglycemia over an extended period can accelerate the onset of these complications (6). Detection of these complications during the initial diagnosis of diabetes is crucial, as it precedes the onset of pervasive impacts on various organs within the body, ultimately contributing to elevated morbidity and mortality rates (7,8).

The progressive nature of T2DM is a notable characteristic that leads to a gradual escalation of treatment options, starting from lifestyle modifications and oral antidiabetic medications, and eventually culminating in insulin therapy (9,10). Hence, many individuals with T2DM eventually discover that insulin therapy is an effective approach for managing their blood glucose levels. Insulin therapy, among the extensive array of treatment modalities available for diabetes, is widely recognized as the most efficacious agent for lowering glucose levels, addressing both acute and chronic elevations in blood glucose (11). Over the past century, insulin therapy has undergone various stages of development, resulting in a diverse range of insulin types with characteristic pharmacokinetic (PK) and pharmacodynamic (PD) that are now accessible to diabetic patients. This diversity provides a broad spectrum of options and regimens that can be tailored to suit different patient-related conditions (12).

Patient-reported outcomes (PROs) emerge as invaluable instruments, especially in the realm of chronic conditions like diabetes, providing profound insights from the patient's perspective across diverse facets of the disease. The true value of PROs was acknowledged in the early 1970s through studies that underscored the significance of patients' reports in enhancing overall patient care (13). One application of PROs involves elucidating symptoms, treatment responsiveness, psychological well-being, and health-related quality of life (HRQOL) (14). The multifaceted data derived from PROs serves as a pivotal resource, alongside clinical outcomes, to guide adjustments in
therapeutic approaches, informing clinical decisions, and facilitating the modulation of various aspects pertinent to patient care (15).

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This review aims to offer insights into diverse insulin preparations and regimens, considering their variable PK and PD properties for effective diabetes management. Additionally, the review seeks to analyze PROs across clinical trials associated with distinct insulin regimens, especially in individuals with type 2 diabetes, providing a comprehensive overview of the impact of insulin therapy on treatment satisfaction and HRQOL. Furthermore, the investigation of PROs aims to identify and understand factors influencing adherence to insulin therapy, offering guidance to both patients and clinicians in addressing these factors to enhance overall adherence to insulin therapy.

**INSULIN PREPARATIONS**

Insulin therapy has undergone significant development and innovation over the past century, from the isolation and purification of pancreatic extracts to the utilization of recombinant DNA technology to produce insulin analogs (16,17). These
advancements have greatly improved diabetic clinical care and patient outcomes. Nowadays, there is a wide range of insulin formulations available, each with unique PK and PD properties. Understanding these properties is crucial for optimizing blood glucose control and avoiding adverse events such as hypoglycemia. Clinicians must possess knowledge of tailored PK and PD properties of insulin to ensure safe and effective prescribing practices for their patients (18).

The physiology of endogenous insulin is substantial in understanding the rationale behind different exogenous insulin preparations. In a healthy individual, the pancreas regulates glucose homeostasis through continuous basal insulin secretion controlling adipocyte lipolysis and liver glucose production, along with peaks of insulin secretion after meals to manage postprandial glucose levels (19). Insulin, secreted as a prohormone by pancreatic beta-cells, undergoes proteolytic cleavage and is regulated by zinc and calcium ions for molecular assembly, structure, and stability. Endogenous insulin secretion is feedback-regulated based on blood glucose levels (20). However, exogenous insulin adjustments lack this feedback mechanism, relying on monitoring blood glucose and considering carbohydrate intake (21). This understanding forms the foundation for developing optimized basal and bolus insulin formulations through bioengineering advancements to enhance PK and PD effects.

The time-action profiles of insulin preparations are determined by the absorption and distribution kinetics that occur after injection. When comparing different insulin formulations, parameters such as onset of action, duration of action, and peak time are important for pharmacometrics evaluations. These parameters are influenced by various factors, including local blood flow to the injection sites in subcutaneous (SC) tissue and the kinetics of insulin molecules transitioning from the SC depot to the bloodstream (12,22). Manipulating molecular features of insulin through recombinant DNA technology and the choice of formulations, including suspensions or hexameric solutions, play a role in determining the duration for insulin to enter systemic circulation (17,23). For instance, insulin formulations in the hexameric form have interactions that bind the molecules together in the SC space. Stronger interactions
delay the dissociation of hexamers into monomers, resulting in a longer onset and duration of action. Conversely, weaker interactions lead to faster dissociation of hexamers and a shorter onset and duration of action (Figure 2). Additionally, it is possible to modulate insulin therapy in SC tissue by modifying insulin formulations with variable excipients and controlling the stability of hexamer molecules (24).

Figure 1: Dissociation of the insulin hexamers in long-acting (degluvec) and rapid-acting (aspart). Slow dissociation of insulin degludec multi hexamers results in prolongation of onset and duration while rapid dissociation of insulin aspart hexamer results in fast onset and short duration of action.

Bolus (prandial) insulin analogs

Bolus insulin analogs demonstrate a more rapid onset, shorter duration, and quicker peak time of action compared to regular human insulin (Table 1) (25). These properties make them suitable for administration just before or during meals, effectively managing blood glucose levels. The reduced duration of action of bolus insulin analogs reduces the risk of postprandial hypoglycemia, which commonly occurs when blood sugar levels tend to be lower after a meal (26). The time-action profile of regular human insulin demonstrated limitations, characterized by a delayed onset and prolonged duration relative to endogenous insulin (Table 1) (27). This resulted in an elevated risk of hypoglycemia before and after meals, accompanied by variability among individuals and within the same individual, presenting challenges in dosing and a heightened probability of hypoglycemic events. (27,28). To overcome these issues, the development of bolus insulin analogs with tailored properties was necessary to enhance the clinical experience of mealtime insulin therapy and reduce the incidence of hypoglycemia (17,26). It has become evident that rapid-acting insulin analogs yield superior outcomes in terms of reduced hypoglycemic events, improved postprandial blood glucose control, and lower HbA1c levels when compared to regular human insulin (29,30).
Bolus insulin analogs have been designed to accelerate self-disassociation and rapid release of monomers from the SC injection site. These analogs differ from human insulin by one or two amino acids, facilitating their faster onset of action (Figure 2) (31). Insulin lispro and insulin aspart are examples of rapid-acting insulin analogs that exhibit a quicker onset compared to regular human insulin. This is achieved by modulating the intermolecular interactions of insulin dimers, weakening the binding forces between them (32). Consequently, the hexameric structures of insulin analogs dissociate more rapidly into monomers, facilitating their release into the bloodstream. On the other hand, insulin glulisine, another rapid-acting insulin analog, employs polysorbate 20 as a stabilizer instead of zinc (Figure 2) (33). Polysorbate 20 acts as a surfactant, preventing insulin molecules from aggregating. This unique stabilization mechanism allows insulin glulisine to be formulated as monomers or dimers, eliminating the delayed onset of action observed with hexameric insulin preparations (34,35).

In addition to modifications to insulin amino acids, the integration of excipients assumes a pivotal role in the development of insulin formulations featuring distinct time-action profiles and enhanced efficacy, particularly in the management of post-prandial glucose, in comparison to rapid-acting insulins (36). The incorporation of excipients aimed at improving SC blood flow, such as vitamin B3 and L-arginine, has given rise to formulations like ultra-fast aspart (FIAsp®) (37). Similarly, the inclusion of agents like Treprostinil or Biochaperone, designed to augment vascular permeability or diffusion mechanisms as observed in ultra-rapid lispro (URLi), has yielded insulins with faster onset compared to rapid insulin analogs (38).

Table 1 Different types of insulin with their brand names and pharmacodynamic properties.

| Basal insulin preparations |

The main goal of developing basal insulin preparations is to achieve a consistent and steady time-action profile that closely resembles the behavior of endogenous basal insulin. Various means have been employed since the inception of insulin to extend its
availability from SC space into systemic circulation, resulting in diverse basal insulin formulations with distinct time-action profiles. Neutral Protamine Hagedorn (NPH) insulin, introduced in 1946, represents one such intermediate-acting formulation with a delayed onset (approximately 1-3 h), a late peak (around 4-6 h), and a duration of action lasting approximately 13-18 h (Table 1) (53). Over time, the utilization of NPH insulin has uncovered notable drawbacks. Its limited duration of action, reaching a maximum of 18 h, impedes its feasibility for once-daily administration in a considerable patient population (54). When administered at bedtime for nocturnal basal coverage, the delayed peak of NPH poses the risk of inducing hypoglycemia during the early morning hours (55). Furthermore, the inherent unpredictability in NPH's absorption and activity contributes to intra-individual variability in insulin levels, leading to fluctuations in plasma insulin concentrations and, subsequently, unforeseen episodes of hypoglycemia and undesired hyperglycemia (19,56,57). In addition, the wide variability in de-precipitation at the injection site further adds complexity to its predictability and absorption (58).

To address the limitations of NPH insulin in meeting basal insulin requirements, the development of basal insulin analogs through recombinant DNA technology has emerged. Categorized into two generations, the first includes insulin glargine-100U/mL (Gla-100) and insulin detemir (IDet), while the second comprises insulin glargine-300U/mL (Gla-300) and insulin degludec (IDeg) (59). Introduced in 2000 under the brand name Lantus® by Sanofi, Gla-100 is a synthetic analog of human insulin distinguished by modifications at positions A21 and B31/B32 (Figure 2), enhancing its solubility in acidic pH and resulting in an increased isoelectric point to 6.7. Upon SC injection, Gla-100 undergoes micro-precipitation in the injection depot due to exposure to higher physiological pH, followed by slow dissolution into monomeric form before entering the circulation system (60). This mechanism yields a time-action profile for Gla-100 that is flatter, more stable, and consistently without noticeable peaks over 24 h compared to NPH insulin (16). Clinical trials have provided evidence that transitioning from NPH insulin to glargine leads to enhanced glycemic control, as indicated by
decreased fasting blood glucose levels and a reduction in episodes of nocturnal hypoglycemia (61,62).

**Figure 2 Basal and bolus insulin analogs with their structural modifications**

Insulin detemir (IDet), marketed as Levemir®, is another first-generation long-acting basal insulin analog that received FDA approval in 2005. Structurally, it differs from human insulin by incorporating a 14-carbon myristoyl fatty acid to the lysine at B-29, while eliminating the C-terminal threonine amino acid at B-30 (Figure 2). Upon injection, IDet molecules self-associate into di-hexamers, prolonging their persistence in the SC space by delaying hexameric dissociation. Moreover, the fatty acyl side chains of IDet enable its binding to albumin, resulting in delayed distribution to peripheral tissues and elimination from the body (46). Compared to insulin glargine, IDet has a shorter duration of action, leading to reduced glucose-lowering activity in the second 12 h following administration (63). Furthermore, IDet exhibits lower potency, requiring higher doses and more frequent injections in obese type 2 diabetic patients, typically following a twice-daily regimen reflecting the lipophilic nature of insulin detemir molecules (16,64).

The second generation of basal insulin analogs, including insulin Gla-300 and IDeg, surpasses the first generation by offering flatter, more predictable, and longer-lasting insulin profiles. FDA-approved in 2015 and marketed as Toujeo® by Sanofi, Gla-300 is a concentrated form of Glargine-100 with an identical molecular structure (16). Upon SC injection, Gla-300 exhibits equipotent dosing to Gla-100 but with a reduced volume, resulting in a more compacted SC depot and a decelerated, gradual, and extended release of Gla-300 monomers into circulation, persisting for up to 36 h (23). Clinical trials indicate that Gla-300 offers a less pronounced glucose-lowering effect than Gla-100 but with a more stable profile, reduced variability, and enhanced physiological modulation capacity (65). Therefore, type 2 diabetic patients may require a 12% higher dose of Gla-300 than Gla-100 for equivalent glycemic control, and a 20% reduction in dosage is recommended when transitioning from Gla-300 to Gla-100 to mitigate the risk of hypoglycemia (17,66).
Insulin degludec, commercially known as Tresiba® (Novo Nordisk), gained FDA approval in 2015 as a synthetic analog of human insulin. Distinguished by its extended duration of action, lasting up to 42 h at steady state, insulin degludec undergoes structural modifications by replacing the threonine amino acid at position B30 with a side chain containing glutamic acid and a 16-carbon fatty acid at position B29 (Figure 2) (19). These modifications, in the presence of zinc and phenol as a preservative, facilitate the formation of a soluble and stable di-hexamer. Upon subcutaneous injection, the phenolic preservative diffuses away, and di-hexamers self-associate to form multi-hexamers in the injected depot (Fig.1). Gradual dissociation of multi-hexamers into monomers, coupled with reversible attachment to albumin in the bloodstream, allows insulin degludec to maintain effectiveness for an extended period (67). Studies reveal that insulin degludec achieves comparable glycemic control to insulin glargine, with a reduced incidence of nocturnal hypoglycemic episodes in individuals with type 2 diabetes (68,69).

Insulin Icodec, engineered by Novo Nordisk for once weekly administration, undergoes distinct modifications relative to human insulin. These include the substitution of A14 with glutamic acid, and both B16 and B25 with histidine, coupled with the deletion of Thr30 at B30. Additionally, acylation of B29 involves the addition of a 20-carbon fatty acid to the lysine amino acid (70). These modifications significantly prolong its duration of action by improving proteolytic stability and solubility, concurrently reducing its affinity for insulin receptors and enhancing binding with serum albumin. This reduction in receptor binding and clearance effectively extends the overall action of Insulin Icodec (71). A recent meta-analysis comparing Insulin Icodec with other basal insulin analogs revealed similar efficacy in terms of glycemic indices, accompanied by a slight increase in the risk of hypoglycemia and weight gain associated with the use of Icodec. (72).

Overall, different basal insulin analogs have demonstrated a more physiological insulin delivery profile, characterized by flattened peaks and longer durations of action, compared to intermediate-acting insulin like NPH. This profile has been associated with
a lower incidence of nocturnal hypoglycemic events (17,59,73). Therefore, numerous studies consistently support the use of basal insulin analogs over NPH due to their lower risk of hypoglycemia (26), reduced emergency department visits or hospitalizations related to hypoglycemia (74), and comparable glycemic control with fewer injections (75). Therefore, for individuals aiming to minimize the occurrence of hypoglycemia while maintaining consistent glycemic control, the use of basal insulin analogs is recommended as a preferable option to NPH insulin (76).

*Insulin mixtures*

Intensifying insulin therapy becomes necessary when basal insulin alone is insufficient to achieve glycemic targets. Insulin mixtures, which combine basal and bolus insulins in a single vial or cartridge, offer a solution while preserving their respective pharmacokinetic properties. These mixtures can be formulated using either human insulin or insulin analogs. Biphasic human insulin comprises 70% NPH insulin and 30% soluble human insulin, while biphasic insulin analogs like biphasic insulin aspart (Novomix®) and biphasic insulin lispro (Humalog® mix) are offered in varied concentrations (75/25, 50/50, 70/30), utilizing the protaminated form of each insulin for extended action (Table 1) (77). The widespread popularity of premixed insulin preparations in diabetes management can be attributed to their convenience, as they offer both basal and bolus insulin coverage in a single injection while minimizing the risk of mixing errors (78–80).

The protaminated fraction within premixed insulin formulations introduces inherent limitations to their PK and PD properties, impacting clinical efficacy. This is manifested as the "shoulder effect," an outcome of the interaction between the protaminated fraction and the soluble fraction in the insulin mixture, resulting in undesirably prolonged glucose-lowering effects (81,82). Moreover, variability in insulin action may occur due to the requirement for proper resuspension for accurate dosing and the release of insulin from insulin-protamine precipitates in SC tissue (83–85). To address these limitations, studies have explored the use of a premixed analog co-formulation comprising a combination of two insulin analogs: degludec as
the basal insulin and aspart for bolus coverage (RYZOGEG®). When compared to other premixed formulations, especially biphasic aspart, the premixed analog co-formulation (degludec/aspart) has demonstrated comparable glycemic control while exhibiting lower rates of overall and nocturnal hypoglycemia, along with improved control of fasting blood glucose (52,86).

Biphasic human insulin, although widely used, has notable limitations such as a delayed time to peak effect (1-5 h) and the need for administration 30-45 minutes before meals containing carbohydrates, which can restrict flexibility and patient compliance (78). These regimens are also associated with a higher risk of hypoglycemia compared to basal-bolus regimens due to fixed insulin proportions and less physiological PK (87,88). In contrast, premixed analog formulations have demonstrated reduced occurrences of nocturnal and overall hypoglycemia events, along with improved postprandial glycemic control while achieving comparable HbA1c levels (89-91). When comparing premixed insulin analog regimens, both aspart and lispro have shown similar PK and PD properties, resulting in similar glycemic control and hypoglycemic events (92-94).

Premixed insulin formulations generally provide a decreased frequency of injections compared to basal/bolus therapy, which may be advantageous for some patients. However, it is important to note that premixed insulin therapy requires strict adherence to consistent meal timing and carbohydrate intake, as the insulin components within the formulation cannot be adjusted independently (95). Despite their benefits, premixed insulin formulations have limitations that need to be addressed in order to optimize their effectiveness and improve patient outcomes in the management of diabetes. Further research is warranted to enhance the design and formulation of premixed insulin regimens, taking into account these limitations and striving to achieve optimal glycemic control and patient satisfaction.
INSULIN REGIMENS FOR TYPE 2 DIABETIC PATIENTS

In T2DM patients, the initiation of insulin therapy typically encompasses the administration of basal insulin employing either NPH or an analog (96). If the initial insulin dosage proves inadequate for achieving glycemic targets, a graduated approach is typically adopted, commencing with lower doses and incrementally adjusting to attain the desired glycemic control (97). In cases of insufficient control, the treatment plan is further intensified by incorporating prandial insulin, focusing on meals with significant postprandial glucose excursions. Should the target A1c level remain unattained during follow-up, the treatment strategy undergoes escalation, progressively including prandial insulin doses until a comprehensive basal-bolus regimen is established. This escalation may involve considering premixed insulin regimens or introducing self-mixed/split insulin regimens, all aimed at optimizing glycemic control (98).

The basal-bolus approach, widely regarded as the optimal regimen, closely mirrors physiological processes by providing basal insulin for overnight coverage and eliciting dynamic prandial insulin responses to meals (99-101). However, a unanimous agreement on the most effective or optimal insulin regimen for T2DM patients has not been reached. This assertion is supported by two meta-analyses that thoroughly investigated and compared premixed and basal-bolus insulin regimens in individuals with T2DM who did not attain the desired outcomes with previous treatments (102). One meta-analysis demonstrated similar effectiveness in lowering HbA1c levels between premixed and basal-bolus insulin regimens, especially in T2DM patients initiating insulin therapy for the first time. However, among individuals with prior insulin experience, basal-bolus therapy exhibited superior efficacy in HbA1c reduction, accompanied by heightened insulin requirements and increased body weight, while the risk of hypoglycemia remained unchanged (103). Similarly, another meta-analysis revealed no clinically significant difference in HbA1c reduction between insulin-experienced or insulin-naive type 2 diabetes mellitus (T2DM) patients, with similar
event rates for overall daily insulin dose, hypoglycemia, and weight gain between the compared regimens (104).

A significant divergence in insulin regimens is the number of daily insulin injections that individuals with diabetes approach with caution and careful consideration. However, a comparison of full basal-bolus (2-4 shots/day) with full premixed (2-3 shots/day) insulin regimens, based on the daily insulin injections, revealed no significant difference (P-value = 0.095) in reducing HbA1c levels, regardless of the total number of insulin injections per day (102). Currently, there is a lack of comprehensive research providing sufficient evidence to determine definitively or establish superiority between premixed and basal-bolus regimens for treating type 2 diabetes in patients who have not achieved desired results with previous treatment approaches.

A noteworthy aspect to highlight is that most studies comparing various insulin regimens in patients with type 2 diabetes (T2D) emphasize the importance of a patient-centered approach in selecting the appropriate regimen. This approach involves considering patient preferences and individualized factors such as insulin accessibility, complexity, and flexibility. Clinicians should take these factors into consideration to tailor the treatment and adapt it according to the specific needs of each patient (102,105–108).

PROS AND PROS MEASURES (PROMS)

PROs are self-reported measures that provide valuable insights into the impact of chronic health conditions and treatments on individuals' daily lives. They assess various dimensions of health, including physical functioning, emotional well-being, treatment satisfaction, and health-related quality of life (109,110). PROs are increasingly being incorporated into research studies and routine clinical practice (111), enabling better understanding of the patient experience and facilitating personalized care. Studies related to PROs provide valuable information that can be implemented in clinical decision-making. This data serves a dual purpose: it not only informs and
improves individual patient care but also facilitates comparisons and enhancements in the overall quality of care delivered (112). Embracing shared decision-making and considering patient preferences in treatment selection aligns with recent guidelines advocating for a patient-centered approach to diabetes care (113,114). This emphasis on patient preferences is likely to have significant implications for the future use of PROs in evaluating healthcare services (110,115).

Patient Reported Outcome Measures (PROMs) offer a valuable approach for measuring PROs. PROMs consist of standardized and frequently validated questionnaires that enable the assessment of a patient's health status at a specific moment, whether during the course of an illness or while managing a health condition (116). Their valuable role emerges in guiding clinicians and researchers seeking to gain insights into the experiences of patients with diabetes (117). These tools are utilized to assess various aspects of diabetic patients' lives, including treatment satisfaction, medication adherence, self-management abilities, and overall quality of life (118). In the research field, questionnaires serve as effective tools for several reasons as they enable the collection of data from a large number of individuals in a convenient and efficient manner (119). Moreover, PROMs provide a standardized approach to gather patient experiences, ensuring that results can be easily compared between different patient groups in a validated manner (120). Unlike conventional measures like clinical laboratory data, PROMs offer a more comprehensive understanding of patients' overall life experiences (14). Additionally, they offer the opportunity to identify patients who may be struggling to manage their condition and to evaluate the effectiveness of new treatments and interventions (121).

Several questionnaires have been developed for the purpose of collecting PROs. The choice of questionnaire depends on the specific needs of the patient and the research objectives. In the context of diabetes and its treatments, numerous questionnaires exist to assess the impact of the disease on various aspects of quality of life (QOL). For instance, a recent systematic review examined 17 questionnaires that target different life domains affected by diabetes, including physical, psychological, emotional, and social
aspects (120). The review revealed significant variability among the available questionnaires in terms of validity and language availability. This diversity offers researchers a range of options to measure QOL, allowing them to select the most appropriate questionnaire based on their research question and the characteristics of the population being studied. Apart from the 17 questionnaires mentioned, there are several others used to assess the impact of diabetes on various life domains, which can be categorized as either generic or diabetes-specific questionnaires. Commonly utilized generic questionnaires include the Short Form 12 or 36 (SF-12 or SF-36), EuroQOL 5 dimensions (EQ-5D), Hospital Anxiety & Depression Scale (HADS), International Physical Activity Questionnaire (IPAQ), and Work Productivity & Activity Impairment (WPAI) (122-127). On the other hand, diabetes-specific questionnaires such as the Diabetes Productivity Measure (DPM) and the Diabetes Symptom Checklist - Revised (DSC-R) have also been employed in various studies (128,129). Compared to generic questionnaires, diabetes-specific questionnaires provide more standardized measures to evaluate the effects of diabetes on different aspects of life, including general well-being, mental health, productivity, and symptomatology.

When investigating the impact of different insulin types on QOL, researchers have a variety of options to assess patient satisfaction levels and the effects of treatment on QOL. Similar to the questionnaires used to assess the impact of diabetes on QOL, questionnaires utilized to evaluate patient satisfaction and the effects of insulin therapy can be generic, encompassing all diabetes medications, or specific to insulin treatments. Commonly used generic questionnaires for assessing insulin effects include the Patient-Perceived Difficulties in Diabetes Treatment (PDDT), Patients' Perceptions About Medications for Diabetes (PAM-D), and Diabetes Medication Satisfaction (DiabMedSat) questionnaires (129-131). Among them, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) is widely employed to evaluate patients' satisfaction with insulin therapy (132-140). However, since researchers require sensitive tools capable of detecting differences arising from variations in insulin types or delivery devices, several questionnaires specifically designed to assess the effects of insulin therapy have been
developed. For instance, the Insulin Treatment Satisfaction Questionnaire (ITSQ) has demonstrated validity and reliability in assessing satisfaction levels with different insulin therapies (141). The Insulin Treatment Experience Questionnaire (ITEQ) has proven effective in identifying QOL differences associated with various insulin therapies (142). Additionally, the Experience With Insulin Therapy Questionnaire (EWITQ) and Expectations about Insulin Therapy Questionnaire (EAITQ) were developed to provide insights into the expectations and experiences of insulin therapy specifically for individuals who are new to insulin treatment (143). Moreover, the Insulin Therapy-Related Quality of Life (ITR-QOL) questionnaire, which is validated and widely utilized, assesses the effects of insulin therapy on different aspects of life. Overall, the wide array of available questionnaires, along with other assessment tools, offers researchers and HCPs valuable resources to enhance the QOL of individuals with diabetes by optimizing insulin therapy based on PROs (142).

**QOL AND DIABETES**

QOL encompasses a comprehensive and multidimensional concept that comprises an individual's subjective assessment of their physical, emotional, and social well-being (144). The significance of QOL in managing chronic diseases, such as diabetes, is pivotal, impacting patients' capacity to deal with their condition and sustain overall well-being (145). Therefore, when formulating treatment plans and interventions for diabetes management, considering the impact on QOL is essential. Numerous studies and guidelines emphasize the importance of addressing QOL in diabetes management. The recent guidelines from the ADA recommend HCPs to acknowledge the influence of diabetes on QOL and provide necessary support and resources to help patients overcome related challenges (146).

Diabetes has long been known to take a toll on the QOL of those who live with it (144,147). This negative impact is not limited to one aspect of the patients' lifestyle but it can extend to deteriorate various dimensions, including physical, emotional, social and financial sides (148). Diabetes, as a chronic disease, is known for its association with
various physical complications, such as atherosclerotic cardiovascular diseases (ASCVD), nephropathy, neuropathy, and retinopathy, causing pain and limitations in daily activities, thus adversely affecting QOL (149–151). Emotionally, managing diabetes can result in anxiety and stress due to the constant need for blood glucose management, regular medication intake, and symptom and complication monitoring. These demands can significantly impact both the emotional and physical well-being of patients (152). Social functioning and relationships of diabetic patients may also be affected due to changes in diet, exercise routines, and daily activities (153). Additionally, the financial burden associated with the costs of medications, supplies, and healthcare services for diabetes management can cause stress and limit access to resources, further negatively impacting QOL (154). Considering these factors, recent guidelines emphasize the significance of prioritizing QOL as a key treatment objective which is now recognized as the fifth component within the glycemic pentad framework, providing guidance for healthcare professionals in making informed treatment decisions (155). It is crucial for clinicians and HCPs to recognize that the effects of diabetes extend beyond metabolic changes and disease complications, significantly impacting various aspects of patients' lifestyles.

Effects of insulin therapy and different regimens on QOL:

The widely acknowledged understanding that living with diabetes, as a chronic condition, can have a negative impact on QOL becomes even more intricate when insulin therapy is incorporated into patients' treatment regimens. Insulin therapy introduces an additional factor that has the potential to influence QOL in either positive or negative ways (128,156). Therefore, we conducted a comprehensive investigation of relevant literature in the PubMed database, with a particular focus on studies that included PROs. Predefined keywords, such as "insulin therapy," "PROs," "Questionnaire", "type 2 diabetes", and "quality of life," were utilized, employing variations and combinations to ensure a comprehensive search. The inclusion criterion for this study encompassed research conducted since 2000, aligning with contemporary developments in diabetes management. The objective was to comprehensively evaluate
the impact of insulin therapy on the QOL in individuals with type 2 diabetes. The results of this study, summarized in Table 2, revealed both positive and negative effects of insulin therapy on QOL. On one hand, it has proven efficacy in managing hyperglycemia symptoms and improving metabolic control, particularly for patients unresponsive to previous treatments (157–159). It has demonstrated effectiveness in mitigating the occurrence of diabetic complications, consequently leading to enhancements in various aspects related to quality of life and overall well-being (160–162). In addition, Initiation of insulin therapy has been shown to yield favorable outcomes across various domains related to QOL, encompassing psychological, physical, and social aspects (Table 2) (132,133,163–167). A recent study proved that diabetic patients who receive insulin therapy with treatment adherence and more diabetes-related knowledge showed improvement in QOL scores when compared with diabetic patients treated by oral medications alone (168). Furthermore, studies have shown that such enhancements extend beyond the realms of QOL, as they are accompanied by a notable increase in treatment satisfaction (Table 2) (128,132–134,169–171), thereby underscoring the significance of initiating insulin therapy as a comprehensive and efficacious intervention.

On the other hand, studies comparing insulin users to non-insulin users consistently reveal lower QOL scores among insulin users across mental, physical, social, and overall health dimensions (Table 2) (124,165,172–175). Moreover, insulin users have reported lower levels of treatment satisfaction compared to those who do not incorporate insulin into their treatment regimens (176,177). These unfavorable effects on QOL can be attributed to adverse events associated with insulin therapy, such as increased fear of hypoglycemia and negative impacts related to weight gain (123,178,179). Furthermore, the incorporation of insulin therapy may elicit feelings of stigma among individuals with diabetes, fostering a perceived loss of control over their own disease management (180).

Overall, an intriguing observation emerges when examining various studies that explore the positive and negative effects of insulin therapy on QOL depending on
PROMs, as presented in Table 2. Studies showing unfavorable QOL outcomes among insulin users primarily adopt a comparative approach, contrasting them with non-insulin users. Conversely, studies reporting favorable results in terms of satisfaction and QOL tend to focus on the impact of insulin therapy in a longitudinal follow-up manner, with only two studies including a direct comparison between insulin users and non-insulin users (166,168). These findings underscore that the prolonged use of insulin therapy is linked to enhanced glycemic control, leading to a reduced incidence of diabetic complications and improved quality of life (162,181).

Table 2 Studies assess the effect of insulin therapy on satisfaction and QOL.

The selection of an optimal insulin regimen tailored to individual patients' needs is a crucial aspect of providing effective diabetes care. Guidelines stress the importance of thoroughly assessing various factors when deciding to initiate insulin therapy, including age, overall well-being, mental status, life expectancy, presence of complications, and feasibility of different insulin formulations (188). It is also recommended that diabetic patients have a good understanding of different insulin regimens, diligent glycemic control monitoring, and the process of selecting the most suitable formulation for effective treatment (189).

When commencing insulin therapy, HCPs have the option to choose between premixed insulin or basal insulin depending on the specific clinical situation. While the American Diabetes Association (ADA) suggests starting with basal insulin, there are cases where patients may benefit from beginning with premixed insulin. These situations can include when a patient's HbA1c level is above 8.5%, when patients struggle with the complexity of a basal-bolus regimen, or when fasting blood glucose levels are below 150 mg/dL but HbA1c remains elevated (190,191). Studies comparing the start of premixed and basal insulin therapies in patients with type 2 diabetes have shown that premixed insulins provide better control of blood sugar levels compared to basal insulin alone. However, it is important to note that using premixed insulin increases the risk of experiencing hypoglycemia episodes and gaining weight (191,192).
Premixed insulin regimens offer a simplified approach to insulin therapy as they contain pre-formulated combinations of short-acting and intermediate- or long-acting insulin. These combinations demonstrate a safety and effectiveness profile that is comparable to basal-bolus regimens. Additionally, they offer the advantage of necessitating fewer injections, thereby contributing to a reduction in the complexity of the overall insulin regimen (193). As an option, it is appropriate for patients who have regular and routine eating habits or who may have difficulty counting their carbohydrate intake. In addition, it offers advantages over self-mixed insulin, providing more precise dosages, greater effectiveness, and improved patient convenience (49,194). It can also be a preferred option for individuals who find it challenging to adhere to the demands of basal plus or basal-bolus regimens due to the reduced injection frequency and monitoring associated with premixed insulin (195). Furthermore, premixed insulin can help alleviate insulin distress, which can hinder optimal glycemic control, as it involves less intrusion and improves patients' willingness to adhere to the treatment regimen (153).

Despite these advantages, premixed insulin formulations have limitations in terms of dosing flexibility, as they do not allow for independent adjustment of insulin dosage between the long-acting and short-acting components. They are also found to be less effective than full basal-bolus regimens in achieving targeted HbA1c levels (106,196). Moreover, the use of premixed insulin is associated with an increased risk of hypoglycemia, weight gain, and a higher likelihood of experiencing adverse events, which may make it unsuitable for regular use in elderly individuals (197–199). Additionally, the sole long-acting insulin used in most premixed formulations, NPH, has certain drawbacks in its time-action profile that can affect the regimen's efficacy and safety (200).

On the other hand, The basal-bolus insulin regimen, also referred to as multiple daily injections (MDI), is commonly regarded as the preferred regimen due to its ability to closely replicate the natural secretion pattern of insulin (201). This regimen provides patients with flexibility in terms of varying mealtimes and carbohydrate content. It has
the potential to maintain a consistent 24-hour glucose profile and achieve the same level of HbA1c as conventional insulin regimens (202). However, the basal-bolus regimen can be complex, requiring patients to accurately count carbohydrates and adjust insulin dosages accordingly, which can be challenging and time-consuming (203). Regular and diligent blood glucose monitoring is necessary for individuals on the basal-bolus regimen. It also requires patients to possess knowledge of insulin-carbohydrate ratios and correction factors, enabling them to make necessary adjustments to their insulin dosages for achievement of desired glycemic control. This regimen emphasizes the importance of patient involvement and understanding in managing their diabetes (191).

A recent study found that patients who discontinued the basal-bolus regimen often cited its complexity as the main reason for non-adherence. In addition, challenges in calculating bolus doses, managing food intake in relation to bolus insulin, and keeping track of administering two different types of insulin were reported (204).

Given the current lack of conclusive evidence regarding the superiority of premixed and basal-bolus insulin regimens in the treatment of type 2 diabetes, it becomes essential to explore PROs to shed light on the preferable regimen that minimizes detrimental effects on patient QOL. Conducting investigations that prioritize PROs can offer valuable insights into the experiences and preferences of patients, aiding in the comparison of both insulin regimens and guiding the selection of the most suitable regimen for individual patients. Our comprehensive research involved a systematic search within the PubMed database, targeting studies conducted since the year 2000 that specifically focused on PROs comparing premixed and basal-bolus insulin regimens. The search utilized variations and combinations of specific terms, including "insulin therapy," "PROs," "Questionnaire," "premixed," and "basal-bolus." The primary objective was to identify an in-depth analysis of the comparative outcomes associated with these two insulin regimens with detailed results of PROs have been meticulously presented in (Table 3). Some studies showed that patients treated with the basal-bolus regimen reported higher treatment satisfaction compared to those on the premixed regimen (136,205). While some studies demonstrate that the basal-bolus
regimen is associated with improvements in HRQOL and reduced psychological fear of hypoglycemia (136,137,205-207), other studies indicate that patients report favorable outcomes in HRQOL with premixed insulin regimens (127,208,209). Nevertheless, several studies found no significant difference in treatment satisfaction and various domains of quality of life between the two regimens (100,129,131,138,139,210). The variations in reported outcomes among diabetic patients can be attributed to factors such as the utilization of diverse questionnaires in different studies, which differ in complexity, length, and focus, leading to a broad spectrum of conclusions. Additionally, individual perceptions of inconvenience and pain associated with insulin injections can vary significantly, leading to variations in treatment satisfaction (211). Patients' perceptions of insulin therapy may be influenced by the complexity of various treatment regimens, contributing to variations in outcomes (212). Moreover, variations in metabolic responses to different insulin regimens among different ethnic and racial groups can directly impact patients' reactions to these regimens (213).

It is crucial to acknowledge the distinction between clinical trials and real-world settings when evaluating the effectiveness of different insulin regimens. This distinction emphasizes the need to consider real-life factors and patient experiences alongside clinical trial findings to gain a comprehensive understanding of treatment outcomes. Clinical trials typically select participants with higher compliance rates and provide more intensive monitoring, which may not reflect the conditions faced by patients in real-world scenarios. Therefore, the outcomes observed in clinical trials may not always accurately reflect the performance of these insulin regimens when used by patients with varying levels of adherence and follow-up in real-world situations (106,190).

Table 3 Studies comparing premixed and basal-bolus regimens in term of patient-reported outcomes.

**ADHERENCE TO INSULIN THERAPY**

For patients with type 2 diabetes receiving insulin therapy, adhering to their prescribed medication regimen significantly impacts their ability to manage blood
glucose levels effectively (214). Extensive research has demonstrated that inadequate medication adherence and persistence, coupled with suboptimal glycemic control, can lead to adverse clinical outcomes, including an elevated risk of cardiovascular events, morbidity, and premature mortality (159,215). Conversely, improved adherence to insulin therapy yields better glycemic control and reduced healthcare resource utilization (216). Studies consistently show a positive correlation between adherence to insulin therapy and achieving adequate glycemic control in diabetic patients. Recent studies using novel technology also proved by that nonadherence to insulin therapy results in poor glycemic control that cause higher HbA1c (217,218). Despite this fact, many diabetic patients discontinue or interrupt insulin therapy shortly after starting (219).

Achieving target glycemic control in diabetes requires patients to exhibit two key behaviors: adherence and persistence. Adherence to therapy refers to the degree to which patients follow the instructions and recommendations of their healthcare providers, including taking medications at the right dose, time, and duration (220). It is the responsibility of HCPs to develop an insulin regimen that is feasible for patients to implement, while patients are responsible for complying with the treatment plan. Adherence to insulin therapy poses distinct challenges, with a significant proportion of type 2 diabetic patients (44.3%) not adhering to this treatment, leading to suboptimal glycemic control and increased risks of complications (221). Persistence, on the other hand, relates to the length of time patients adhere to their prescribed treatment regimen (222). In simpler terms, HCPs must keep writing prescriptions for the medicines that patients need, and patients must keep getting those prescriptions filled and taking the medicines as prescribed. However, studies have demonstrated that merely 20% of individuals who start basal insulin treatment continue with it for a full year (219). Non-persistence with insulin therapy can also have negative consequences, including inadequate glycemic control and an elevated risk of diabetic complications, which aligns with the impact of non-adherence (219). In addition, studies have revealed that poor adherence to insulin therapy is prevalent, with rates reaching up to 86% in certain
patient populations, depending on the measurement methods employed and the characteristics of the population under investigation (10). Furthermore, adherence to insulin therapy may differ depending on the specific insulin regimen being utilized. For example, an investigation utilizing insurance claims data in France revealed distinct treatment persistence rates: 61.8% for basal insulin, 15.0% for fast-acting insulin, and 23.2% for other insulin regimens (223). Additionally, the frequency of insulin administration can also impact both persistence and adherence to insulin treatment (223,224). A survey conducted with both patients and physicians highlighted that the most significant challenges and concerns affecting adherence to insulin treatment were related to the frequency and precise timing of insulin injections (225). Numerous studies have consistently demonstrated that the complexity of insulin regimens, especially those involving a higher number of injections, directly impairs adherence to insulin therapy (226-231). Additionally, the perception of insulin therapy by patients and HCPs can have a significant impact on adherence. Therefore, factors influencing adherence to insulin therapy can be categorized into three primary domains: patient perceptions of insulin therapy, HCP perspectives on insulin therapy, and the patient-HCP relationship.

**Patient-related factors affecting adherence to insulin therapy:**

Research indicates that patient adherence to insulin therapy is intrinsically linked to their perceptions and beliefs (232). The determinants of these attitudes encompass a wide range of factors, including insulin-related beliefs, psychological considerations, hypoglycemic concerns, and barriers to therapy. These factors significantly impact patients' willingness to use insulin as a treatment for diabetes. Beliefs about insulin, influenced by illness severity, cultural perspectives, and specific notions associated with insulin, can affect patients' acceptance and utilization of this therapy (233,234). Furthermore, cultural beliefs that do not align with prevailing beliefs about insulin and diabetes management can hinder adherence to insulin therapy (235).

Psychological factors also play a significant role in patients' perception of insulin therapy. These factors include fear and anxiety related to hypoglycemia, pain from
injections, and weight gain (236,237). Studies have shown that some diabetic patients experience shame and self-blame, believing that they caused their illness and that their need for insulin is a result of poor diabetes control. Depression has been found to have a significant impact on insulin use, particularly in relation to the fear of self-injecting. Research suggests that depression is a strong predictor of this fear. Negative emotions have also been identified as obstacles to successful self-care strategies in patients with low activation in self-management (238). In addition, patients reported difficulty injecting insulin in front of others due to concerns about making them feel uncomfortable or offended. Some patients may experience anxiety or fear related to injections, resulting in avoidance of insulin injections due to anxiety (211).

Many surveys conducted among diabetic patients have identified hypoglycemia as a significant barrier that affects their emotional state, daily activities, and ability to adhere to insulin treatment (239,240). As a result, patients may inject smaller doses of insulin to avoid hypoglycemia, which can lead to poor treatment adherence or omission (241,242). Additionally, the occurrence of hypoglycemic events, particularly nocturnal hypoglycemia, can significantly disrupt various aspects of diabetes self-management, including sleep quality, work performance, driving abilities, and overall personal well-being (243). Moreover, research has indicated that these events can also lead to negative financial implications and a decline in overall quality of life (240).

The complexity of managing insulin therapy poses challenges that can hinder adherence to insulin treatment. Numerous surveys have established links between non-adherence and practical obstacles, including difficulties with injections and inflexible treatment regimens (214,244). Patients may omit insulin injections due to uncertainty about whether a dose has already been administered (245). Titration of insulin doses is another complex aspect that some patients struggle with. Studies indicate that patients often ignore instructions or adopt their own approach to titration (241,242,245,246). Some patients preferred to have HCPs make insulin changes, while others preferred to have control over their own insulin regimen. In addition, it was
proven that type 2 diabetic patients commonly experience a high medication regimen complexity index, which adversely affects medication adherence and leads to poor glycemic control (233). In contrast, patients with low or moderate medication regimen complexity have shown to have improved adherence and better glycemic control (227). These findings suggest that patients may face varying challenges and barriers to adherence based on the type of insulin regimen prescribed.

Social influences play a significant role in adherence to insulin therapy. The perception of stigma associated with publicly injecting insulin can greatly impact adherence. Patients may be concerned about being judged by others who associate insulin injection with drug addiction (247). Moreover, the influence of family and friends on a patient's management of their insulin treatment can also affect adherence. Some patients find it challenging to adhere to their insulin use due to family mealtime routines and requirements, while others recognize the positive impact of having family support in managing their diabetes (246). Many patients perceive that insulin therapy negatively affects their participation in travel, leisure, and social activities. They express concerns about restrictions on their social interactions and feel that their insulin injection behavior is influenced in social settings due to the requirements of insulin therapy (234). The social implications of insulin therapy are particularly notable in low- and middle-income countries, where individuals and healthcare systems may face significant financial burdens due to limited access to affordable insulin. The rising costs of insulin in recent years have put a strain on patients who rely on this medication to manage their diabetes (248). The high costs associated with insulin can lead patients to ration their medication or skip doses, resulting in adverse health outcomes and escalating healthcare expenses over time (249). Additionally, there are other expenses related to insulin therapy, such as glucose monitoring supplies and healthcare provider visits. Insulin-dependent patients may also experience indirect costs due to missed work or reduced productivity related to managing their diabetes (250).

Numerous effective approaches have been identified to address factors that negatively impact patients' perceptions of insulin therapy. Notably, research indicates
that culturally tailored interventions within the context of diabetes management can successfully address cultural beliefs associated with insulin therapy. These interventions specifically target cultural factors and beliefs, with the aim of improving patient understanding, acceptance, and adherence to insulin therapy (251,252). Addressing the complexity and practical barriers associated with different insulin regimens and their impact on medication adherence is crucial for healthcare providers (HCPs) to customize interventions and support strategies for individuals receiving insulin therapy. Artificial intelligence (AI) shows promise in overcoming practical obstacles by identifying problematic glycemic patterns and providing effective insulin dosage recommendations. This has the potential to enhance adherence to insulin therapy, thereby preventing life-threatening complications associated with insulin treatment (253). Moreover, the presence of positive social and family support has been strongly linked to effective adherence to diabetes management. Addressing social barriers becomes essential, and fostering social and family support systems becomes crucial in ensuring optimal adherence to insulin therapy (254).

HCPs-related factors affecting adherence to insulin therapy

Another area that mainly affects adherence to insulin therapy is the perception of HCPs to the insulin therapy and their relationships to the patients. One crucial aspect is the competence required by primary care HCPs to initiate and manage insulin therapy effectively, as well as provide ongoing support to individuals with diabetes. Some HCPs expressed a lack of confidence in handling insulin-related issues and emphasized the importance of training and continuous guidance from diabetes specialists (255). HCPs recognized that patient-level factors strongly influenced insulin usage and believed that patient education positively influenced adherence. Furthermore, HCPs have noted that insulin treatment can be perceived by certain patients as a symbol of failure or progression to a more advanced stage of their illness, potentially impacting their behavior. Patient behavior regarding insulin therapy is often influenced by subjective emotions and perceptions, rather than solely focusing on treatment objectives (256). Various reasons for low adherence to insulin therapy have been identified by
HCPs, including patients' busy schedules, travel commitments, challenges in timing meals, stress or emotional issues, fear of public embarrassment, and patients' perception of their diabetes control. Understanding these factors and collaborating with patients to address them are crucial for HCPs to enhance adherence to insulin therapy (257).

The adherence to insulin therapy in diabetic patients is influenced by the quality of the rapport with HCPs. The nature of this rapport can have either positive or negative effects on patients' insulin behaviors, depending on factors such as the HCP's communication skills when discussing insulin-related information, their responsiveness to patient concerns, the duration of consultations, and the accessibility and relevance of the support provided (233,258). Additionally, the divergent agenda between HCPs and patients is an important aspect of their relationship. While HCPs often prioritize achieving tight glycemic control, patients place greater emphasis on their overall QOL and broader life needs. Patients may modify their behavior to try to appease HCPs, reflecting the different priorities and concerns between the two groups (246).

Research has demonstrated that HCPs can enhance patient adherence to insulin therapy through various means. Key strategies include effectively demonstrating the insulin injection process, adopting a collaborative approach in decision-making, emphasizing the benefits of insulin, and addressing patient concerns and misconceptions. Encouraging patient collaboration in developing a shared action plan is highlighted as a valuable approach, while an authoritarian communication style that repeatedly attempts to persuade patients to initiate insulin therapy is considered to be the least helpful. These findings provide important insights for HCPs aiming to improve patient adherence to insulin therapy (259).

Adherence to insulin therapy is impacted by the cost of insulin therapy, which patients and healthcare providers need to consider. Studies have revealed that a significant proportion, up to two-thirds, of diabetic patients, particularly in low-middle income countries, report skipping insulin doses due to the inability to afford the cost of insulin (260). Addressing the cost-related barriers to insulin therapy adherence requires a multi-faceted approach. This includes discussing affordability with patients, raising
awareness about available resources, integrating cost considerations into practice guidelines, promoting the use of lower-cost biosimilars, and advocating for policies that ensure affordable access to insulin. By implementing these strategies, both patients and HCPs can work towards improving adherence to insulin therapy despite financial constraints (261).

This review acknowledges several significant limitations that should be taken into account when considering its findings and implications for future research. Firstly, the absence of conclusive evidence favoring either premixed or basal-bolus insulin regimens based on PROs poses a challenge due to inconsistent and inconclusive results observed across different studies. This diversity in outcomes hinders the formulation of definitive recommendations regarding the superiority of one regimen over the other. Secondly, the inclusion of studies employing different questionnaires with varying focuses and complexities introduces heterogeneity and makes it difficult to effectively compare and synthesize the findings. The lack of standardized measurement tools across studies contributes to the limitations of the review. Furthermore, the reliance on data primarily derived from clinical trials raises concerns about the applicability of the findings to real-world settings characterized by lower compliance and monitoring. The controlled environment of clinical trials may not fully capture the complexities and challenges experienced by individuals in their everyday lives. Additionally, while the review identifies factors influencing adherence, the causal relationships and interplay between these factors remain unclear. Further research is needed to gain a more comprehensive understanding of the intricate mechanisms governing patients’ adherence behaviors.

In summary, it is crucial to recognize that by equipping healthcare professionals with essential skills, offering support, and embracing a patient-centered approach, there is the potential for fostering positive relationships and achieving improved outcomes in insulin therapy for patients. Collaborative efforts between HCPs and diabetic patients are essential in addressing adherence barriers and formulating strategies to improve adherence. This patient-centered approach plays a significant role in achieving optimal
glycemic control and reducing the likelihood of diabetes-related complications. While the current understanding of adherence and PROs in insulin therapy for type 2 diabetes has yielded valuable insights, expanding the research scope is vital. Future investigations should explore a wider range of insulin options beyond the traditional focus on premixed and basal-bolus regimens. Additionally, standardized PRO questionnaires tailored to insulin users are crucial for ensuring consistent and comparable data across studies. This would facilitate robust comparisons and enhance the reliability of research findings. Understanding subjective factors influencing adherence and QOL will inform personalized interventions and support strategies. Furthermore, real-world data from diverse clinical settings, obtained through electronic health records and patient registries, is necessary to accurately depict adherence patterns and translate research findings into practice. Evaluating the cost-effectiveness of different insulin regimens alongside their impact on both adherence and QOL is crucial for informing resource allocation and policy decisions. Finally, developing targeted interventions for specific patient groups, considering factors like age, cultural background, and comorbidities, can significantly improve adherence and patient-centered outcomes.

CONCLUSION

Insulin therapy has witnessed significant advancements over the past century, resulting in a wide range of insulin preparations with distinct PK and PD properties. This diversity has given rise to various insulin regimens, contributing to a considerable variability in treatment approaches. However, there is currently no universally optimal insulin regimen that HCPs can employ for all patients with type 2 diabetes. Consequently, it is imperative to investigate PROs using different PROMs to assess the impact of insulin therapy on patient satisfaction and QOL. Further research is warranted to address conflicting findings from diverse clinical trials and explore the influence of insulin therapy on QOL based on PROs. HCPs should demonstrate a keen interest in individualized patient needs and preferences regarding insulin therapy
while possessing a thorough understanding of factors affecting adherence to different insulin regimens, taking into account active feedback from patients.

REFERENCES