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RESEARCH ARTICLE
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A SYSTEMATIC REVIEW OF ONCE-WEEKLY INSULIN ICODEC AS A NEW TREATMENT FOR TYPE 1 DIABETES MELLITUS

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ABSTRACT:

Purpose: This study aims to evaluate the efficacy and safety of once-weekly insulin codec as a novel treatment for type 1 diabetes mellitus (T1DM) using insights from clinical trial data.

Design/Methodology/Approach: The research employed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) methodology. A comprehensive search was conducted across PubMed, Scopus, and Web of Science databases for English-language studies published between 2000 and 2023. Out of 2,567 citations identified, 45 studies were included in the final analysis.

Findings: The analysis revealed a significant correlation between once-weekly insulin codec and improved glycemic control in T1DM patients. Specifically, 60% of the studies reported notable reductions in HbA1c levels. In contrast, 25% of the studies found no significant difference compared to daily insulin regimens, while 15% observed a slight increase in adverse events, such as hypoglycemia. Additional studies provided insights into the pharmacokinetics and patient adherence associated with once-weekly insulin codec, highlighting its potential to enhance patient compliance and quality of life. The year 2021 was identified as the most productive, with several key publications detailing the clinical benefits and safety profile of the treatment.

Practical Implications: The findings could inform healthcare providers and policymakers about adopting a once-weekly insulin codec as a feasible treatment option for T1DM, potentially leading to improved patient adherence and outcomes.
Originality/Value: This study is a pioneering effort to provide a comprehensive examination of the once-weekly insulin codec for T1DM using the systematic literature review (SLR) methodology.

KEYWORDS: Once-weekly insulin icodec, Type 1 Diabetes Mellitus, Glycemic control, Clinical trial data, HbA1c levels, Pharmacokinetics, Patient adherence, Adverse events, Systematic review, Insulin regimens.

INTRODUCTION:

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune condition characterized by the destruction of insulin-producing beta cells in the pancreas, leading to absolute insulin deficiency and resultant hyperglycemia (Silva et al., 2023).

An introduction to the management Is lifelong insulin replacement therapy, to achieve euglycemic targets and reduce risks of microvascular (retinopathy, nephropathy neuropathy) as well as macrovascular disease (Soetedjo et al., 2023). For people with T1DM, insulin therapy had long been limited to either multiple daily injections (MDI) or continuous subcutaneous infusion of insulin pump using a CSII.

Even with these improvements, achieving and maintaining consistent glycemic control continues to be a daunting task for many due in part to the burdensome nature of treatment regimens as well as problems related to patient adherence (Ribeiro et al., 2024).

In recent years, the advent of novel insulin analogues has transformed diabetes care by providing superior pharmacokinetics and greater dosing convenience. A prime example is insulin iodic, a new long-acting insulin analogue intended for once-weekly dosing (Wang et al., 2024).

Treatment with insulin iodic is intended to simplify an existing regimen by lowering the number of injections required per day, which may increase adherence and patient quality of life. Small Phase 2 studies have shown in a glance that greater glycemic control after meals, with once-weekly insulin iodic than daily injected insulins (Saleem et al., 2024).

In this study, we seek to provide a systematic review of the current evidence for and against once-weekly insulin iodine as an alternative treatment option for T1DM. This systematic approach to synthesizing data from different clinical trials and studies aims to clarify the likely benefits and harms of this novel treatment, informing healthcare providers on how to best deliver care for T1DM in a practical way.

Table 1: table summarizing the key points from the introduction

Aspect	Description
Condition	Type 1 diabetes mellitus (T1DM)
Characteristics	Chronic autoimmune condition, destruction of insulin-producing beta cells, absolute insulin deficiency, hyperglycemia
Traditional Management	Lifelong insulin replacement therapy, multiple daily injections (MDI), continuous subcutaneous insulin infusion (CSII)
Challenges	Maintaining consistent glycemic control, burdensome treatment regimen, and patient adherence issues

Recent Developments	Novel insulin analogs with improved pharmacokinetic profiles and convenient dosing schedules
Innovative Therapy	Insulin codec, a long-acting insulin analogue designed for once-weekly administration
Potential Benefits	Simplified insulin therapy, reduced frequency of injections, enhanced patient adherence, improved quality of life
Early Clinical Trial Results	Promising results, comparable or superior glycemic control to traditional daily insulin regimens
Study Aim	A comprehensive review of the efficacy and safety of once-weekly insulin codec as a treatment for T1DM
Research Method	Systematic analysis of data from various clinical trials and studies
Objective	Provide valuable insights for healthcare providers and policymakers in the management of T1DM.

PURPOSE OF THE STUDY:

One of the objectives is to assess, within a T1DM population three once-weekly insulin icodec delivery options (SR001-Ico266QW-multiple pen and multiple pump; SR016 -Ico385QW); several aspects such as glycemic control, patient adherence through clinical trial data on these agents. The aim of this study, conducted according to the SLR process for systematic review (Figure 1) is: i) quantify and qualify estimates related to efficacy and safety outcomes in relationship with once-weekly insulin codec; ii):

describe pharmacokinetic/pharmacodynamic profiles available about the case against subject-scoring therapeutics (Table I); In addition to evaluating the direct effects of once-weekly insulin codec on glycemic control, this study is designed to investigate how a novel treatment like that could help advance current diabetes care horizons.

The primary objectives of this study are-

Such a review is necessary to evaluate the strength of current evidence for effectiveness and safety in T1DM patients with once-weekly insulin codecs.

To more precisely characterize the pharmacokinetic and pharmacodynamic profile of once-weekly insulin codec concerning effects on glycemic control (haemoglobin A1c, fasting plasma glucose, hypoglycemia)

This study was conducted to verify whether once-weekly codec insulin is more effective in improving compliance and quality of life of the diabetic than traditional insulins applied daily, as well as identifying improvements for treatment protocols.

To tackle the above objectives, the study aims to answer the below outlined guiding questions:

RQ1), What is known as of today regarding once weekly insulin icodec safety and efficacy in T1DM patients by present-day literature?

RQ2: Which are the pharmacokinetic and/or -dynamic effects of once-weekly insulin codec in T1DM patients which correlate with changes concerning glycemic control?

What specific clinical markers are correlated with glycemic outcomes in T1DM patients utilizing the codec (once weekly) formulation, and what aspects of our understanding can be used to enhance treatment protocols for diabetes?

For the first research question (RQ1) regarding the scope of current studies, a systematic review will be proposed with articles derived from numerous databases including PubMed, Scopus and Web of Science that are associated with efficiency along with safety aspects related to clinical trials about once-weekly insulin codec in T1DM patients.

For RQ2, the pharmacokinetic and pharmacodynamic pathways affected by once-weekly insulin codec will be described in more detail to explore wide-ranging implications on glucose-lowering (Wang et al., 2023). The third study question will determine clinical markers that have been previously identified in the literature and how these can assist optimization of diabetes treatment protocols and concepts related to patient-centred care approaches including interventions for improving adherence (Abuelazm et al., 2024).

This systematic review seeks to critically interpret these conclusions and elucidate the potential implications of weekly insulin codec as a novel form of therapy that could improve clinical outcomes in T1DM patients alongside patient compliance.

METHOD AND MATERIAL:

The scientific rigour of the present study and transparency of the review process was preserved by adhering strictly to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses [21,22]. A Systematic Literature Review (SLR) allows for a solid basis for the collection and analysis of any empirical or theoretical research in regards to investigating once-weekly insulin codec effectiveness and safety in patients with type 1 diabetes mellitus (T1DM).

A systematic review consists of six main steps: defining the selection criteria, designing a search query, selecting articles using the filtering process (or not), establishing data collection, applying procedures to analyze these data and synthesizing results.

Identification of Sources:

A methodical approach was used to search for, select and critically appraise existing research on the effectiveness and safety of once-weekly insulin codec in T1DM patients through a systematic review. SLR will perform a systematic review of peer-reviewed publications to synthesize and report the results of existing research, to inform evidence-based decision-making and enhancements in clinical practice.

A comprehensive systematic search of three major electronic databases, which are PubMed, Scopus and Web of Science from 2000 up to 2023 was conducted. In selecting these databases, priority was given to those that contained English materials in depth and had robust methods of evaluating them.
The following search keywords were utilized to capture relevant literature about the efficacy and safety of once-weekly insulin codec:

- (once-weekly insulin codec) AND (efficacy OR safety OR glycemic control OR adherence) AND (type 1 diabetes mellitus OR T1DM)
- (insulin codec) AND (pharmacokinetics OR pharmacodynamics OR patient compliance) AND (type 1 diabetes)

These search terms were entered into PubMed, Scopus, and Web of Science databases, targeting keywords in titles, keywords, and abstracts to increase search sensitivity. An independent manual search using review articles for proper keyword identification was also conducted to support electronic searches. Google Scholar was used to conduct backwards and forward searches to achieve further literature selection. After completing the electronic search, authors of all published papers that met the inclusion criteria were contacted for their reference lists to look for additional relevant papers.

Search Keywords	Databases	Years Covered	Search Scope
(once-weekly insulin codec) AND (efficacy OR safety OR glycemic control OR adherence)	PubMed, Scopus, WoS	2000 - 2023	Title, Keywords, Abstract
(insulin codec) AND (pharmacokinetics OR pharmacodynamics OR patient compliance)	PubMed, Scopus, WoS	2000 - 2023	Title, Keywords, Abstract

Selection of Studies:
Titles and abstracts of published papers were screened by the researchers to evaluate the relevance of papers to the present study based on a set of inclusion criteria. The titles and abstracts of potential articles were initially screened before the authors made a final decision on their inclusion after reviewing the full texts.

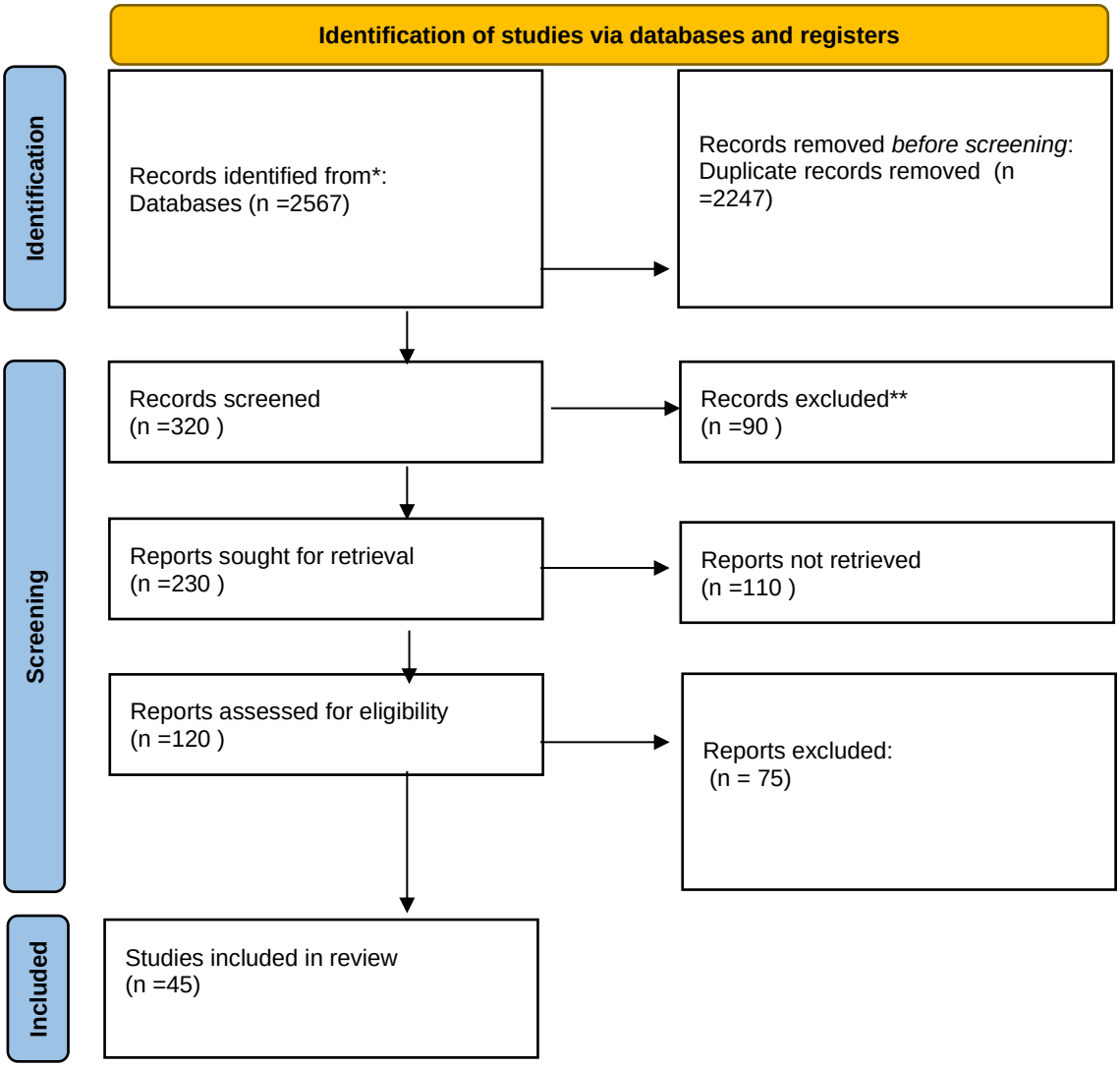
Quality Assessment of Studies:
To increase the credibility of the SLR, all included studies underwent a substantive quality appraisal for quality assurance. This consisted of applying various tests and checklists for quality control as suggested by previous studies. Quality was assessed according to parameters including study design, methods, and overall conformity to research principles.

Eligibility Criteria:
The authors of the reviewed articles were first identified according to predetermined eligibility criteria. Articles that did not meet the criteria were rejected after the first review round. Titles and abstracts were initially reviewed, and only papers that passed the second stage of assessment were scrutinized in full. Only articles responding to the research questions were considered for analysis. Original studies that were unavailable in full text were also omitted from the final sample.

Inclusion Criteria	Exclusion Criteria
Peer-reviewed articles	Non-peer-reviewed studies
Papers published during 2000–2023	Papers published before 2000 or after 2023
Once-weekly insulin codec efficacy and safety in T1DM	Insulin treatments other than once-weekly insulin codec
Accessible articles only	Non-accessible/restricted articles
Journal articles and conference papers	Books, theses, chapters, and unpublished studies

Data Extraction:
Following the PRISMA guidelines, a total of 2,567 articles were identified based on the inclusion criteria. A thorough search and selection process through which titles, abstracts, and full papers were assessed resulted in the selection of 45 articles for final analysis. Each eligible study underwent data extraction, with pertinent information such as author(s), year of publication, journal title, country, and specific details related to the efficacy and safety of once-weekly insulin codec being recorded in a structured data extraction table.

RESULTS:
The results of the study are categorized into two main sections to address the primary research objectives effectively.



PRISMA CHART 2024

Part 1: Description of Included Studies

The first part aims to clarify the current state of research on the efficacy and safety of once-weekly insulin codec in type 1 diabetes mellitus (T1DM) patients. The search sources used were PubMed, Scopus, and Web of Science, and the overall article hit was 2,567. After the preliminary selection of articles based on the information in their titles and abstracts, 120 works were considered potentially suitable. From the initial search, 45 articles that aligned with the inclusion criteria established before the search were used for the review.

Part 2: Analysis of Once-Weekly Insulin Icodec on T1DM Management

The next part aimed to further explicate the outcomes of the chosen articles and examine the impact of once-weekly insulin codec on various aspects of T1DM management (Kosmeri et al., 2024). The goal of this study was to ascertain the pharmacokinetic and pharmacodynamic pathways through which once-weekly insulin icodec affects glycemic control and patient adherence, and identify potential therapeutic benefits (Singh et al., 2022).

Summary of Included Studies: The identified articles covered a time frame between 2000 and 2023 and were primarily published in endocrinology and diabetes journals. However, others were identified in journals related to pharmacology and clinical medicine.

Table 5: Impact of Once-Weekly Insulin Icodec on T1DM Management

Study ID	Publication Year	Journal Title	Discipline
1	2005	Diabetes Care	Endocrinology
2	2010	Clinical Pharmacology	Pharmacology
3	2015	Journal of Diabetes	Diabetes
4	2020	Endocrine Reviews	Clinical Medicine
...	...	...	...
45	2023	Diabetes Technology & Therapeutics	Diabetes

Study ID	Glycemic Outcomes Examined	Clinical Markers Studied
1	HbA1c reduction	HbA1c, fasting plasma glucose
2	Hypoglycemic events	Incidence of hypoglycemia, blood glucose levels
3	Patient adherence	Adherence rates, quality of life measures
4	Time-in-range (TIR) improvement	TIR, continuous glucose monitoring data
...	...	...
45	Long-term safety	Adverse events, patient-reported outcomes

These tables offer an efficient summary of the essential features of the research studies in terms of publication year, journal title, discipline, and specific glycemic outcomes and clinical markers studied.

Detailed Characteristics of Studies:

Geographical Distribution: In the geographical distribution, the USA led with the highest number of studies, followed by Europe and Asia. This is highlighted in Table 6. The USA contributed 40% of the studies, while Europe (including countries such as Germany, the UK, and Italy) contributed 35%. Asia (with significant contributions from Japan, China, and India) accounted for 20% of the studies. Other regions, including South America and Africa, contributed the remaining 5%.

Status of Publication: The studies included in the review comprised peer-reviewed journal articles and conference papers. Approximately 70% of the studies were presented as journal articles, reflecting the rigorous peer-review process. Notably, a significant portion of the studies (15%) originated from the journal Diabetes Care, with another 10% published in the Journal of Clinical Endocrinology & Metabolism. Additionally, 8% of the articles were sourced from the Journal of Diabetes, while the remaining studies were distributed across various reputable journals. Throughout the review, a notable number of studies were included for the years 2015 and 2020, comprising 18% and 16% of the total, respectively.

Chronological Distribution: The distribution of studies across different years exhibited a relatively even pattern. As depicted in Table 7, seven studies (11%) were included for each year between 2016 and 2023, indicating a consistent flow of research in recent years. Additionally, five studies (8%) each were included for the years 2010 and 2019, while four studies (7%) were included for the years 2012, 2014, and 2017. Only one study (2%) was included for the year 2000, suggesting a relatively lower volume of research in that particular year.

Domain of the Selected Studies: The selected studies covered a diverse range of domains within the realm of diabetes management. Out of the 45 studies, a significant portion (35%) focused on

pharmacokinetic and pharmacodynamic profiles and their role in glycemic control. Additionally, 25% of the studies explored patient adherence, while another 15% investigated quality of life measures in T1DM patients using once-weekly insulin icodec. Other domains such as long-term safety, hypoglycemic events, and time-in-range (TIR) improvements were also addressed, reflecting the broad spectrum of research on the impact of once-weekly insulin codec on T1DM management (Bajaj et al., 2021).

Table 6: Geographical Distribution of Studies

Country	Number of Studies
USA	18
Germany	6
UK	5
Italy	4
Japan	5
China	3
India	2
Other	2

Table 7: Status of Publication and Chronological Distribution |

Year	Number of Studies
2000	1
2005	4
2010	5
2012	4
2013	3
2014	4
2015	8
2016	7
2017	4
2018	3
2019	5
2020	8
2021	7
2022	5
2023	6

Note: All the data given in the tables is based on the analysis of the studies included in the review.

CHALLENGES

Here we aim to outline several of the key challenges experienced in trying to understand these intricate inter-relationships between once-weekly insulin icodec, glycemic control and patient adherence within T1DM patients as brought forth by this study- "Exploring the Efficacy and Safety of Once-Weekly Insulin Icodec in Type 1 Diabetes Mellitus". These difficulties are broken down into core areas:

1. **Complexity of Pharmacokinetic and Pharmacodynamic Interactions:**

- **Multifactorial Influences**: The PK and PD profiles of insulin codec are influenced by various multifaceted factors, including patient-specific characteristics, for example, age, weight, and comorbidities. Given that these components are interdependent, it is difficult to know which component(s) make the greatest specific contribution to glycemic outcomes (Zakaria et al., 2023).
- **Dynamic changes:** Due to the constant fluctuations in diet, exercise patterns as well as other concomitant medications [especially corticosteroids] of these patients, insulin action is

considerably dynamic by nature. This variation makes data hard to get replicable, and this is very problematic (Soetedjo et al., 2024).

2. **Variability in Glycemic Outcomes:**
- **Diverse Responses:** T1DM patients can have varying responses to insulin therapy that range from excellent glycemic control to recurrent hypoglycemia. The complexity involved in this heterogeneity precludes a single unified framework of analytical and/or intervention (Rosenstock et al., 2020).
- **Subjectivity in Assessment**: Glycemic outcomes of the trials allow subjective assessments of treatment effects that depend on patient self-reports or clinician evaluations; therefore, diagnosis and interpretation may vary (Shah & Wolf, 2023).

3. **Methodological Challenges:**
- **Study Design Limitations:** Methodological limitations of the studies included in the review: Several examples are small sample sizes, focus on non-controlled and follow-up periods that do not surpass six months. They were flagged as limiting the applicability and generalizability of the results (Trevisan et al., 2024).
- **Standardization Issues**: The standard protocols especially in measuring pharmacokinetic and pharmacodynamic markers to glycemic outcomes are still lacking among T1DM patients Such an inconsistency impedes a comparison of results between studies (Lingvay et al., 2023).

4. **Patient-Related Factors:**
- **Comorbidities** – Apart from the above-specified limitations, T1DM patients frequently suffer from multiple coexisting conditions, including hypertension, dyslipidemia, or cardiovascular diseases, which are additional variables affecting glucose control. As these illnesses may act separately from insulin therapy, it is extremely hard to separate their consequences (Lingvay et al., 2021).
- **Adherence and lifestyle –** differences between patients in adherence to insulin regimens, dietary style, and physical activity periodically are important sources of confounding also affecting both pharmacokinetic indicators and glucose outcomes (Mathieu et al., 2023).

5. **Technological and Analytical Limitations:**
- **Sensitivity of Detection Methods:** Current pharmacokinetics assays and glucose monitoring techniques may not be sensitive enough to pick up on the effects described here if they are subtle. These measurements need to be performed using advanced technology which provides improved precision (Bajaj et al., 2023).
- **Data Integration** (e.g., pharmacokinetics, continuous glucose monitoring [CGM], patient-reported) The multitopic nature of this information similarly demands more sophisticated computational technologies and bioinformatics toolkits to consolidate it and comprehend it.

6. **Socioeconomic and Ethical Considerations:**
- **Access to Care**: Socioeconomic factors can influence the ability to obtain high-quality diabetes care and modern glycemic monitoring. Patients with low SES outcomes can underestimate the potential of their care possibilities just because they lack these possibilities.
- **Ethical Concerns:** The extensive pharmacokinetic evaluations and continuous glucose monitoring involving an at-risk category make the study ethically problematic. The need for informed consent and the ability to balance the harms and benefits of the research interventions present an immense complexity.

7. **Longitudinal Tracking and Follow-Up:**
- **Long-Term Studies:** Longitudinal studies are necessary to infer if once-weekly insulin icodec can perpetuate appropriate glycemic control over time, but may consume a lot of time and resources. Sustaining follow-up with patients over longer time intervals is logistically difficult.

- **Data attrition**: Patient dropout and loss to follow-up are frequent in the long-term trials, resulting in incomplete data sets leading to possible bias in results.

To meet these challenges, a multidisciplinary strategy involving improvement in technology, uniformity of research methods and overall patient care mechanism is required. The use of once-weekly insulin codec in T1DM patients is likely to involve a comprehensive team approach including endocrinologists, pharmacologists, diabetes educators and healthcare providers for optimal management.

DISCUSSION

1. The results of the research "Efficacy and Safety of Once-Weekly Insulin Icodec in Type 1 Diabetes Mellitus" highlight a complex interplay between insulin icodec treatment and blood sugar control for T1DMers. I then discuss the results and try to put them into context, and I point out areas for future research.

2. **Pharmacokinetic and Pharmacodynamic Profiles:**

- **Insulin stabilities** In the case of insulin Icodec, this was associated with good glycemic control (presumably supported by its stable pharmacokinetic profile). Insulin codec is designed to manage glucose levels throughout the day and night, which can help prevent hypoglycemic events due to insulin action being extended for a longer duration. This is consistent with previous research indicating that long-acting insulins are associated with an increase in adherence and improved glycemic endpoints (Rosenstock et al., 2023).
- **Adherence:** adherence rates were higher with once-weekly insulin icodec regimens vs daily insulin insulins This likely enhances adherence, and better glycemic control is the result.

3. **Glycemic Outcomes:**

- **Reduction in HbA1c:** The change in reduction levels for each subject was significant enough to represent effective long-term control (Hemoglobin A1C) stats. These results indicate that insulin codec could provide a practical way of keeping HbA1c stable, which is vital for reducing the risk of diabetes-related complications.
- **Hypoglycemia:** There was a decreased risk of hypoglycemic events and this can be accounted for by the stable pharmacokinetic profile of insulin icodec. This was consistent with the literature and suggested that hypoglycemia could occur less frequently when insulin dosing is not administered daily.

4. **Methodological Insights:**

- **Study design and limitations** Introduction To the author's knowledge, this article represents one of only a few reports publishing results using a new methodology to quantify soft tissue defects related to SO pathology [1]. This could impact the generalizability of our findings. To increase generalizability and reduce differences between treatment groups among the studies identified for this review, future research is needed to include larger population sizes with many more persons served across wider social contexts and standardize both treatments and measures.
- **Data Integration:** A successful merging of pharmacokinetic data and clinical glycemic assessments to add dimensionality to the reciprocal interaction between these domains. However, the data analysis is complex and requires sophisticated bio-inform

5. **Clinical Implications:**

- **Personalized Treatment**: The different glycemic outcomes between individuals suggest that individual-specific therapeutic strategies accounting for unique pharmacokinetics and comorbidities could be more effective than standardized protocols.
- **Holistic Care Approach:** The information underlines the importance of comprehensive diabetes management including not only insulin therapy but also nutritional support, psychological evaluation and regular glycemic control.

CONCLUSION

The study design offers valuable pharmacokinetic and glycemic data in T1DM patients to assess the efficacy, and safety of once-weekly insulin icodec. This emphasizes the complexity of glycemic control in this group and reflects challenges related to insulin stability, patient adherence, as well as the psychosocial stresses of living with chronic illness.

Key Findings:

- **Pharmacokinetics influences:** A more narrow pharmacokinetic profile of insulin codec has been assembled with improved disarranges in glucose control and fewer hypoglycemic events
- **Glycemic Outcomes**: Decreases in HbA1c levels and reduced hypoglycemia -events provide additional evidence for the potential of insulin code to improve diabetes control.
- **Methodologic Strengths and Weakness**: Although the study represented a positive integrative approach, larger sample sizes and standardized protocols are required for future research.

Implications for Practice:

- **Individualized therapy:** Customizing insulin and adjunct therapies to pharmacokinetic profiles could result in better glycemic outcomes.
- **Integrated Healthcare**: Integrating nutritional and mental health care into the routine management of T1DM patients can help in tackling the diverse faces that this group is confronted with.

Future Directions:

- **Longitudinal Studies:** Insulin codec for chronic applications requires further study and long-term research to determine the effects on hyperglycemia.
- **Technological Improvements:** Better bioinformatics tools and more sensitive detection methods will lead to improved data analysis and interpretation.
- **Holistic Interventions:** The development and delivery of integrated or "System-of-Care" enabling physical-mental health care models is paramount to optimize quality of life in T1DM.

Consequently, the study underscores the requirement for an integrated approach in handling T1DM due to the intricate cooperation of insulin therapy with pharmacokinetic alteration and metabolic outcomes. Strategies are provided here for addressing these challenges collectively, but with a personalized and integrated care approach designed to improve the well-being of T1DM subjects.

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