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Effect of fixed-ratio insulin combinations on adherence in type 2 diabetes: Systematic review

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ABSTRACT

Aims: To systematically review evidence on the effect of fixed-ratio combinations on adherence in people with type 2 diabetes.
Methods: Systematic searches were conducted using MEDLINE and EMBASE in March 2023. Standardised screening, data extraction and risk of bias assessment were conducted. All review procedures were conducted independently by two reviewers. Eligible studies assessed the effect of fixed-ratio combinations on adherence in people with type 2 diabetes. Narrative synthesis was conducted to analyse findings.
Results: A total of 488 records were identified, of which 37 proceeded to full-text screening and 7 – each representing a unique study – were included in the systematic review. Among the included studies, 3 were randomised controlled trials and 4 were cohort studies. Following narrative synthesis, it was shown that fixed-ratio combinations improved patient satisfaction and treatment adherence.
Conclusions: Available evidence supports a benefit for fixed-ratio combinations on patient satisfaction and treatment adherence in people with type 2 diabetes.

1. Introduction

Diabetes affects an estimated 10.5 percent of the global adult population, with a total health expenditure of 966 billion US dollars in 2021 [1]. Nearly 90 percent of people with diabetes suffer from type 2 diabetes(T2DM), characterized by insulin resistance [2]. In T2DM, first line treatment usually involves the use of metformin alone or in combination with other oral antidiabetic drugs(OADs), alongside lifestyle and dietary modifications [3]. However, due to the progressive nature of T2DM, initial therapy is rarely enough to maintain adequate glycaemic control, and most patients will need to undergo treatment intensification [4]. As a part of this process, insulin therapy will eventually be required to prevent complications and maintain glycaemic control [5].

Insulin therapy has been shown to improve glycaemic control, reduce the risk of cardiovascular events, and improve life expectancy in the long-term [6,7]. Another major advantage of insulin is its protective effect on pancreatic beta-cells. Insulin causes rapid reversal of glucolipotoxicity and beta-cell rest, preserving and potentially recovering beta-cell function, which may provide long-term health benefits [6]. However, complex insulin regimens increase the treatment burden on patients, as they've been associated with higher rates of hypoglycaemia, weight gain and other adverse effects [8]. While complex regimens can be simplified, the lack of guidance on deintensification of therapy leads to many patients being over-treated, increasing their risk of suffering from adverse effects [8] [10]. Additionally, clinical inertia to insulin initiation remains a challenge, as well as poor adherence to treatment [11]. Patients and healthcare professionals (HCPs) cite factors like treatment complexity and rigidity, increased frequency of self-monitoring blood glucose(SMBG), fear of needles, and fear of hypoglycaemia as some of the main contributors to poor adherence to insulin therapy [11–18]. In these situations, the use of a fixed-ratio combination insulin formulation(FRC) may prove beneficial.

FRCs are a novel class of formulation that combines a long-acting basal insulin with a glucagon-like peptide-1 receptor agonist(*GLP*-1 RA). Several FRCs are currently available globally with evidence showing that they provide equivalent or improved glycaemic control compared to basal insulin(BI), with a lower rate of hypoglycaemia and a positive effect on body weight [8,19,20]. A prospective single-arm clinical trial found that patients who switched to a simpler once-daily regimen of iDegLira had a reduction in mean HbA1c by 0.30 %, with a reduction in mean body weight and BMI by 3.11 kg, and 32.39 respectively [8]. Additionally, The Lixilan-G trial, an open-label

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two-arm parallel randomized controlled trial(RCT), found that patients on iGlarLixi achieved a greater reduction in HbA1c (baseline 7.8 % down to 6.7 %) when compared to *GLP1-RA* therapy [19].The efficacy of FRCs when compared to basal insulin is well established [19–22], however their influence on patients' adherence to treatment is not well documented.

1.1. Rationale

There have been multiple studies conducted which report adherence as an outcome, but to our knowledge, there are no published systematic reviews in the literature on the overall impact FRCs have on adherence to treatment. A systematic review would allow all available eligible evidence to be brought together and presented to show the current state of the evidence base.

The aim of this study was to collect the available evidence on the effect of FRCs on treatment adherence in T2DM to provide a clear picture for HCPs and help guide clinical decisions with regards to insulin therapy.

The key novelty of this manuscript is that it presents the first systematic review to assess the impact of a wide range of fixed-ratio combinations on treatment adherence in type 2 diabetes mellitus. This unique evidence synthesis provides a clear picture for health care providers regarding the current evidence base and helps guide clinical decisions regarding the potential use of fixed-ratio combinations to address typical low adherence rates to standard insulin regimens.

2. Methods

2.1. Design

A systematic review design was used following established Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. All review processes were conducted using standardised forms and were conducted independently by two reviewers.

2.2. Search

Systematic searches were conducted on the MEDLINE and EMBASE databases (Ovid platform) in March 2023. Search terms used a combination of MeSH/EMTREE terms and keywords as appropriate. Searches focused on terms relating to diabetes, insulin and adherence, forming three blocks. Terms within blocks were linked by OR, while blocks themselves were linked by AND. The search and screening process were summarized in the PRISMA flowchart (Fig. 1) with a full detailed list of the search terms used is available in the appendix (Appendix 1, Table S1).

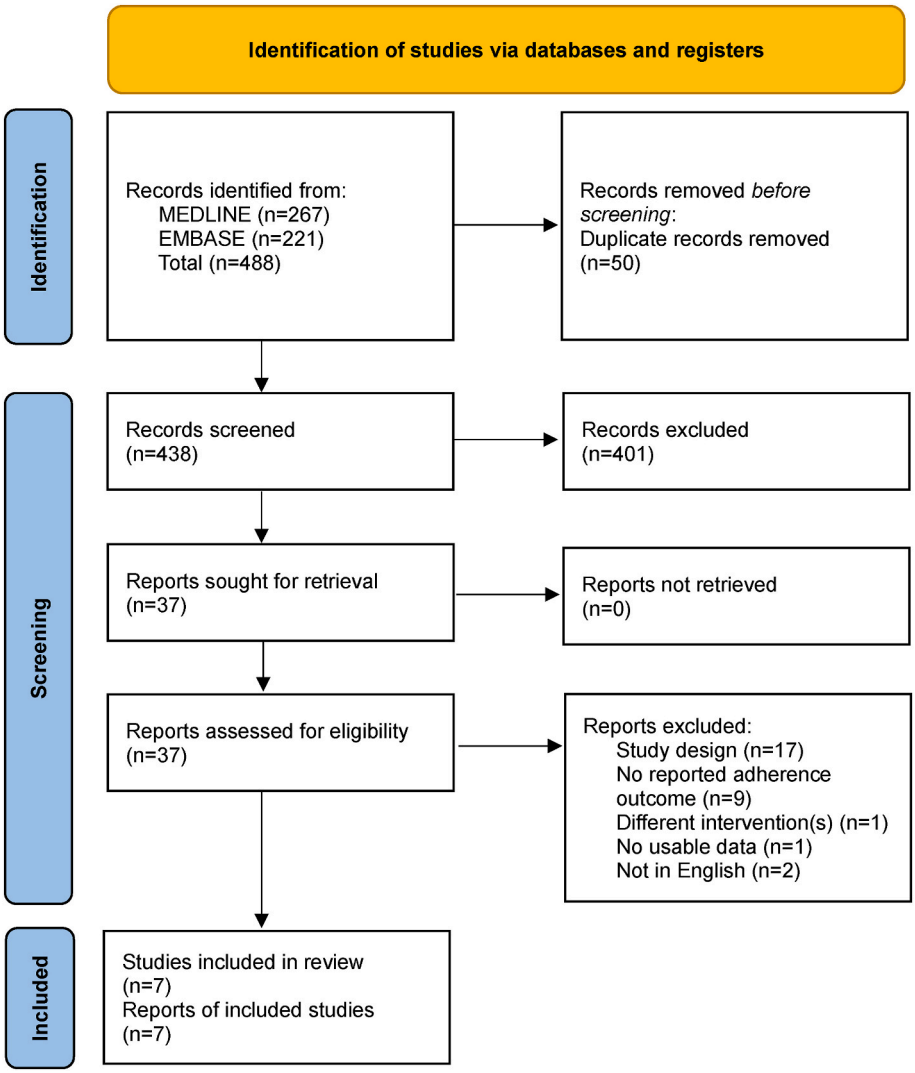

Fig. 1. PRISMA flowchart.

2.3. Screening

Study selection and screening followed a two-step process. First, the titles and abstracts of potentially relevant studies that were identified in the search were screened against previously established population, intervention, control, and outcome(PICO) criteria. These included patients with T2DM as the population, FRCs such as Insulin degludec aspart (IDegAsp), Insulin degludec liraglutide (IDegLira), and Insulin glargine lixisenatide (IGlarLixi) as the intervention, basal insulin, or a placebo as the control if present, and changes in adherence to the treatment regimen as the outcome. Studies without a control or comparator were also included. Second, potentially eligible studies underwent a full review of their text to determine their inclusion. A full list of the inclusion/exclusion criteria is available in the appendix(Appendix 1, Table S2).

This systematic review considered studies published in English from January 1st, 2010 up to the date of the search, with all experimental and observational study designs, both quantitative and qualitative for inclusion. The cutoff date was chosen as such because FRCs were not available prior to this date. Exclusion criteria included type 1 diabetes, gestational diabetes, prediabetes, case reports, case studies, expert opinions, conference abstracts, animal studies, studies published in languages other than English, and studies with no reported outcomes regarding adherence.

2.4. Data extraction

Data extraction was done on the included studies using a standardized data extraction form. Information extracted included data on participants, methods, intervention(s), and outcome(s). For the purposes of this report, we primarily focused on information taken from the published journal articles, with no additional sources being sought unless necessary. Table 1 provides a comparative summary of the study characteristics, with the full data extraction forms available in the appendix (Appendix 2).

2.5. Risk of bias

Risk-of-bias assessment was conducted on each study included. For observational studies, the CASP cohort checklist [23] was used and for randomized-controlled trials (RCTs), the Cochrane RoB-2 tool [24] was used. Tables 2 and 3 provide comparative data summaries of the risk-of-bias assessments done using the CASP checklist and the RoB-2 tool respectively, with the full forms available in the appendix

Table 1
Key characteristics of included studies.

Study	Setting	Population	Methods	Duration	Intervention(s)	Outcome(s)
Lajara et al. (25)	United States	≥18 years old with type 2 diabetes Sample size = 1668	Retrospective Cohort	12 months	iGlarLixi vs. premixed insulin	Treatment persistence, treatment adherence, hypoglycemia events, HRU
Polonsky et al.(29)	Argentina, Austria, Bulgaria, the Czech Republic, Greece, India, Kingdom of Saudi Arabia, Kuwait, North Macedonia, Mexico, Romania, Serbia, South Korea, Spain, Sweden, Taiwan, and Turkey	≥18 years old with type 2 diabetes Sample size = 887	Open-label, two-arm parallel, phase 3b RCT	26 weeks	iGlarLixi vs. BiAsp 30	PROs measured using TRIM-D and GTEE
Miller et al. (28)	12 countries that were not specified	≥18 years old with type 2 diabetes Sample size = 506	Open-label, two-arm parallel RCT	12 months	iDegLira vs. IGlar U100+ IAsp	PROs measured using TRIM-D and SF-36 v2
Melzer-Cohen et al.(26)	Israel	>18 years old with type 2 diabetes Sample size = 413	Retrospective cohort	12 months	iDegLira	Reduction in HbA1c and adherence
Persano et al.(31)	Italy	>18 years old with type 2 diabetes Sample size = 45	Prospective single-arm cohort	6 months	iDegLira	Changes in HbA1c, fasting plasma glucose (FPG), BMI, body weight, cholesterol and triglycerides, blood pressure, type and quantity of insulin and oral therapy taken, occurrence of adverse events, treatment satisfaction, and cost analysis
Rodbard et al.(30)	Algeria, Austria, France, Norway, United States	≥18 years old with type 2 diabetes Sample size = 274	open-label, treat-to-target, phase 3b RCT	26 weeks	iDegAsp vs. IDeg + IAsp	Non-inferiority of IDegAsp versus IDeg + IAsp in change in HbA1c levels, change in fasting plasma glucose (FPG), the proportion of patients achieving HbA1c <7.0 % (53 mmol/mol), change in eight-point SMPG profile, change in mean total daily insulin dose, changes in patient-reported outcomes
Edelman et al.(27)	United States	>18 years old with type 2 diabetes Sample size = 2714	Retrospective cohort	12 months	iGlarLixi vs. free-dose combinations of BI and GLP-1 RA	Treatment persistence, treatment adherence, change in HbA1c, HRU

Abbreviations: RCT: Randomized controlled trial, iGlarLixi: Fixed-ratio combination of insulin glargine and lixisenatide, iDegLira: Fixed-ratio combination of insulin degludec and liraglutide, iDegAsp: Fixed-ratio combination of insulin degludec and insulin aspart, BiAsp30: Biphasic insulin aspart 30/70, iGlar U100: Insulin Glargine U-100, IAsp: Insulin aspart, IDeg: Insulin degludec, BI: Basal insulin, GLP-1 RA: GLP-1 receptor agonist, HRU: Healthcare resource utilization, PRO: patient-reported outcome, TRIM-D: Treatment related impact measure questionnaire, GTEE: Global Treatment Effectiveness Evaluation questionnaire, SF-36 v2: short-form health survey version 2, BMI: Body mass index, SMPG: Self-monitoring plasma glucose.

Table 2
CASP risk of bias comparative table.

Study	Study addressed a clearly focused issue	Cohort recruited in acceptable way	Exposure and outcome accurately measured	Follow up was complete and long enough	Precision of results
Lajara et al.(25)	Yes	Yes	Yes	Yes	• HR = 0.88 • 95 % CI = 0.778–0.998 • P = 00.0465
Melzer-Cohen et al.(26)	Yes	Yes	Yes	Yes	• Mean reduction in HbA1c of 0.65 % • 95 % CI = 0.78–0.52 • P < 0.001
Persano et al.(31)	Yes	Unclear	Yes	Complete: Yes Long enough: No	• HbA1c o 8.4 vs. 7.4 % o p < 0.0001 • Body weight o 94.1 vs. 93 kg o p < 0.0001 • Fasting glycemia levels o 159 vs. 125 mg/dl o p < 0.0001 • DTSQ o mean score: 27 vs. 20 o p < 0.0001 • Average per-patient cost difference o€-0.41 ± 0.59 o p < 0.0001
Edelman et al. (27)	Yes	Yes	Yes	Yes	• Persistence oHR = 1.22 o95 % CI = 1.11–1.35 o P < 0.001 • Adherence o OR = 3.06 o 95 % CI = 2.57–3.65 o P < 0.001

Abbreviations: HR: Hazard ratio, CI: Confidence interval, DTSQ: Diabetes Treatment Satisfaction Questionnaire, OR: Odds ratio.

Table 3
Cochrane RoB-2 risk of bias comparative table.

Study	Domain 1 overall risk of bias	Domain 2 overall risk of bias	Domain 3 overall risk of bias	Domain 4 overall risk of bias	Domain 5 overall risk of bias	Overall risk of bias
Polonsky et al. (29)	Low	Low	High	High	Low	High
Miller et al.(28)	Low	High	Low	High	Low	High (favours experimental)
Rodbard et al. (30)	Low	Low	Low	High	Low	Some concerns (favours experimental)

Favours experimental: Due to the open label design of the study and the subjective nature of the measured outcome, there is a potential for bias that leans in favour of the experimental arm of the study.

(Appendix 2).

2.6. Data analysis

A narrative synthesis was conducted due to the substantial differences between the included studies. Study designs included prospective and retrospective cohorts, both single-arm and two-arm, as well as two-arm parallel RCTs. Populations also varied as these studies were conducted within multiple settings in multiple countries. Interventions varied in terms of which specific FRC was examined, as well as the type of comparator used if available. Outcome measures were equally varied, with multiple studies using different tools for measurements as well as different outcome definitions. The primary method was a textual description of the outcomes of each included study. These descriptions were used to narrative synthesise the findings based on study population, setting, study design and outcome measures. Tabulation of extracted data was done to provide comparative information on study characteristics including population, setting, methods, intervention, and outcomes. The effect on adherence was extracted and summarized for each study to show the potential impact of FRCs on patient adherence.

3. Results

3.1. Search results

From the database searches conducted, 488 total records were identified with 267 and 221 being identified from MEDLINE and EMBASE respectively. After deduplication and initial screening, 37 studies were deemed to be potentially eligible for full-text screening. Of those eligible studies, 7 met our inclusion criteria and 30 were excluded. Reasons for exclusions as well as the number of excluded studies are detailed in Fig. 1.

Of the 7 included studies, 3 were retrospective cohort studies [25] [27], 3 were open-label randomized controlled trials(RCTs) [28–30], and 1 was a prospective single-arm cohort study [31]. All included studies looked at patients 18 years and older, within multiple settings. All cohort studies except one [31] had a duration of 12 months, with the RCTs all having a duration of 26 weeks. 3 studies looked at iGlarLixi [25,27,29], 3 looked at iDegLira [26,28,31], and 1 looked at iDegAsp [30]. 5 of the studies (3 RCTs and 2 cohort) compared a FRC to basal insulin or premixed insulin combinations, with 2 looking at a FRC alone with no comparator. Studies had varying sample sizes ranging from 45 [31] to

1668 [25]. Settings also varied with studies taking place in the US, Israel, Italy, as well as several other European, Asian, and Middle Eastern countries. Key characteristics of included studies are presented in Table 1.

3.2. Risk of bias assessment

For the cohort studies, the potential risk of bias was deemed to be low, with most studies providing accurate exposure and outcome measurements as well as complete follow ups to minimize bias. Adjustments for confounding factors, however, were either unreported or not conducted. For the RCTs, the overall risk of bias was deemed to be high in 2 studies, with some concerns being raised for the third. The main limitation of the RCTs was the lack of blinding (open-label design) which may have resulted in bias of the results, given the subjective nature of the outcome measures. All RCTs mention that blinding wasn't feasible in order to avoid additional burden on patients that can result from having a placebo injection [32] and that masking of the injections wasn't possible [33]. The lack of blinding may not have had a real impact on the results as they are still in line with other available evidence. Risk of bias results are presented in Tables 2 and 3

3.3. Narrative synthesis

Regarding the cohort studies, two looked at iGlarLixi, with the other two looking at iDegLira. Lajara et al. [25], and Edelman et al. [27] reported treatment outcomes among patients who initiated iGlarLixi vs premixed insulin and free-dose combinations respectively, using data from the US Optum Clinformatics database. In both studies, the primary outcome was treatment persistence with adherence being a secondary outcome. Lajara et al. defined persistence as "no discontinuation of the index treatment until the end of the follow-up period, with treatment being considered discontinued if the gap between the run-out date of the previous fill and the next fill was more than 45 days"(25). Edelman et al. defined persistence as "the number of days of continuous therapy from the point of initiation until the end of 12 months of follow-up. Treatment was considered to have been discontinued if the gap between the run-out date of the previous fill and the next fill was more than 45 days"(27). During the 12-month period, a significantly higher proportion of patients were persistent with treatment with iGlarLixi when compared to premixed insulin (42.5 % iGlarLixi vs. 39.1 % premixed; hazard ratio [HR] = 0.88, 95 % confidence interval [CI] = 0.778–0.998; P = 00.0465) [25], with the same being reported when compared to free-dose combinations (44.8 % iGlarLixi vs 36.3 % free-dose; HR = 1.22, 95 % CI = 1.11–1.35; P < 0.001) [27].

In terms of adherence, both studies defined it as the proportion of days covered(PDC), the total days supplied on the claim divided by the number of days in refill interval, using a cutoff of 80 % or more to define adherence and less than 80 % for poor adherence. Lajara et al. found that adherence to therapy across cohorts was similar (41.4 % iGlarLixi vs. 38.0 % premixed; adjusted odds ratio[OR] = 1.15, 95 % CI = 0.95–1.40), with Edelman et al. reporting that adherence to therapy was significantly higher in patients treated with iGlarLixi when compared to free-dose combinations (41.3 % iGlarLixi vs 18.7 % free-dose; OR = 3.06, 95 % CI = 2.57–3.65; P < 0.001).

For iDegLira, Melzer-Cohen et al. [26] and Persano et al. [31] looked at treatment effectiveness and adherence in patients switched from loose-dose injection combinations to iDegLira. Melzer-Cohen et al. conducted a study in Israel and reported adherence as the PDC based on days covered by dispensed prescriptions during the 180 days prior to the index date as well as the first 180 days of treatment, including the titration period [26]. Persano et al. conducted a study in Italy and used a validated version of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) to report patient satisfaction with their treatment [31]. Melzer-Cohen et al. reported that the mean PDC of the group of patients who initiated treatment with iDegLira improved significantly from 60 % (interquartile ratio [IQR] = 34.4–79.4) prior to the index day to 77.8 % (IQR = 65.6–90.0) in the 180 days after the index date(P < 0.01) [26]. The results of Persano et al.'s DTSQ test showed a significant increase in patient satisfaction after switching to iDegLira, with the mean score increasing from 20.1 (14.5–26.5) to 27.6 (25–29; +7.5 ± 5.8; p < 0.0001). The reduction of daily injections and glucose capillary controls were associated with higher satisfaction and greater long-term adherence to treatment [31].

In terms of the RCTs, all three of the included studies were open-label, two-arm parallel RCTs, with each looking at a different FRC. Polonsky et al. [29] looked at patient-reported outcomes (PRO) in type 2 diabetes patients treated with iGlarLixi vs premix BIAsp30, Miller et al. [28] looked at PROs in patients treated with iDegLira vs basal-bolus, and Rodbard et al. [30] reported PROs in patients treated with iDegAsp vs IDeg + IAsp. The Treatment-Related Impact Measure Diabetes (TRIM-D) [28,29], Short Form-36 Health Survey version 2 (SF-36 v2) [28,30], and the Global Treatment Effectiveness Evaluation (GTEE) [29] were used to measure PROs.

For TRIM-D, Polonsky et al. [29] reported that the mean total scores increased from baseline to week 26, going from 68.30(baseline) to 80.46 (week 26) in the iGlarLixi group, and from 67.82(baseline) to 74.97 (week 26) in the BIAsp 30 group. In terms of individual domains, mean scores increased from baseline in both groups, with higher scores in iGlarLixi versus BIAsp 30 at weeks 12 and 26. The effect size (ES) of the change of the total TRIM-D score from baseline to week 26 was large for iGlarLixi (0.85) and small for BIAsp 30 (0.43). For the individual domains, the ESs for change from baseline to week 26 for iGlarLixi were medium in the treatment burden, diabetes management, compliance, and psychological health domains and small in the daily life domain. However, ESs were small across all five domains for BIAsp 30. Miller et al. [28] reported similar findings with TRIM-D. A significantly greater improvement across all five domains, as well as total score, were reported with iDegLira compared to basal-bolus(P ≤ 00.0268). The iDegLira group showed moderate improvements across domains while the basal-bolus group only showed small improvements, with the exception being in the daily life domain. The greatest differences between groups were in diabetes management (estimated treatment differences [ETD]: 10.76, P < 00.0001), treatment burden (ETD: 10.50, P < 00.0001) and compliance (ETD: 6.25, P < 00.0001).

For SF-36v2, Miller et al. [28] reported no statistically significant differences between treatment arms in the physical component summary and domains, however The ETD in change from baseline was significantly higher in the IDegLira group when compared to basal–bolus in the mental component summary (P = 00.0228). There were also greater improvements in each of the mental domains observed with IDegLira but improvement was statistically significant only in the mental health domain (P = 00.0074). Similarly, Rodbard et al. [30] reported no significant differences between groups in the physical component when comparing iDegAsp to IDeg + IAsp, but a higher change in score was observed in the mental score with iDegAsp from baseline. Change in the social functioning score was significantly higher for IDegAsp versus IDeg + IAsp (ETD = 2.2; 95 % CI = 0.3–4.1; P < 0.05).

4. Discussion

4.1. Summary of findings

This systematic review examined the effect of FRC treatment regimens on patient adherence. The review has shown that the effect level is varied among studies, however this may be due to the varying characteristics of the included studies. The studies in included in this review varied in terms of design, population, setting, duration, intervention, and treatment outcomes. For example, two cohort studies looked at adherence in patients being treated with iGlarLixi, with one comparing it to premixed insulin [25], and the other to free-dose combination of BI

and *GLP*-1 RA [27]. Compared to premixed, adherence rates were found to be similar but slightly higher in the iGlarLixi group. However, adherence was found to be significantly higher with iGlarLixi when compared to free-dose combinations. This difference in study characteristics may be one source of the difference in the reported adherence rates.

4.2. Interpretation

For iGlarLixi, treatment persistence was found to be significantly higher when compared to premixed (42.5 % vs. 39.1 %) [25] and free-dose combinations (44.8 % vs 36.3 %) [27]. Adherence rates were found to be similar when compared to premix (41.4 % vs. 38.0 %) [25], but significantly higher when compared to free-dose combinations (41.3 % vs 18.7 %) [27]. Lajara et al. note however, that while the adherence rates were similar in their study, they do not know how many times a day premix insulin was injected [25]. The significant increase in adherence in Edelman et al.'s study suggests that a single once-daily injection of iGlarLixi offers a simpler alternative to a complex multi-injection regimen of a free-dose BI/GLP-1 RA combination. This is supported by previous evidence that shows higher treatment complexity increases the burden on patients [34], with simpler treatment regimens being associated with higher rates of adherence [35,36]. Polonsky et al. reported that the mean total TRIM-D scores increased at week 26–80.46 in the iGlarLixi group, and 74.97 in the BIAsp 30 group [29].These findings demonstrate that iGlarLixi is associated with higher overall treatment satisfaction and lower treatment burden when compared to BI. These improvements were seen regardless of clinical outcomes [29]. Diabetes treatment adherence is impacted by regimen complexity, fear of hypoglycemia, injection fears, and weight gain [13,14,17,34,35,37]. A once-daily regimen of iGlarLixi can provide a less burdensome regimen when compared to twice daily BIAsp 30, encouraging adherence and persistence [29].

For iDegLira, patient adherence significantly improved with PDC of the group of patients who initiated treatment with iDegLira increasing from 60 % to 77.8 % [26]. This shows that in a real-world setting, adherence rates among patients improved after switching from a loose-dose combination regimen to a single-injection regimen of iDegLira [26]. This improvement in adherence was also associated with improved glycemic control among patients, which reinforces the findings of the DUAL VII trial by Billings et al. [22,26]. Persano et al. reported a significant increase in mean DTSQ test scores from 20.1 to 27.6 after switching to iDegLira, which shows higher patient satisfaction with treatment [31]. The reduction in daily injections, absence of adverse effects, reduction in direct costs, and overall simplification of treatment had a positive impact on patient satisfaction and long-term adherence [31]. It should still be noted however, that the small sample size($n = 45$) and lack of a control group present major limitations to the generalizability of these results [31]. Miller et al.'s post hoc analysis of the data from the DUAL VII trial, using TRIM-D and SF-32v2, showed an increase in total score and across all domains for TRIM-D. For SF-36v2, there were no significant differences between treatment arms in the physical component, but the ETD in change from baseline was significantly higher in the IDegLira group when compared to basal–bolus in the mental component of the survey [28]. These findings demonstrate that a simpler treatment regimen results in better PROs, especially in terms of diabetes management, treatment burden and adherence. While patients did not perceive any physical benefits to their treatment when compared to BI, the improvement in the mental component of the SF-32v2 survey showed that patients were more comfortable with iDegLira treatment than BI(28). This is supported by Drummond et al.'s survey of physicians, where respondents showed a greater satisfaction with iDegLira when compared to basal-bolus insulin, and more potential to improve patient motivation as well [38].

For iDegAsp, the SF-32v2 survey findings reported by Rodbard et al. also showed no significant differences between groups in the physical component when comparing iDegAsp to IDeg + IAsp. But, a higher change in score was reported in the mental score with iDegAsp, with a significantly higher score in social functioning for IDegAsp versus IDeg + IAsp (ETD = 2.2) [30]. These findings suggest that iDegAsp had less interference with patients' day to day activities, which can be attributed to the reduction in treatment burden from the simpler regimen [30]. These findings fall in line with the other included studies as well as previously published work showing that a less burdensome treatment regimen is associated with improved adherence. The key clinical relevance of this work is that it addresses the topic of the impact of fixed-ratio combinations on treatment adherence in type 2 diabetes mellitus. The evidence presented in this systematic review may be of interest to physicians treating people with type 2 diabetes mellitus as well as pharmacists.

4.3. Strengths and limitations

To our knowledge, this is the first systematic review to assess the impact of FRCs for insulin delivery on patient adherence in people with T2DM. This advances the state of knowledge by providing a synthesis of available evidence to inform future research and clinical practice. Systematic methods were used to identify and analyse evidence to reduce the risk of bias using the analytical process. In particular, all review processes were conducted independently by two reviewers.

This work was conducted as part of a master's dissertation at the University of Exeter. The timescales for the completion of this academic degree imposed certain limitations, namely that only articles published in English could be considered, that only the two pivotal databases (Medline and EMBASE) could be searched, and that only the class effects of FRCs could be considered rather than considering any differences between individual FRCs in terms of adherence.

4.4. Future directions

Future work could investigate whether there are differences between individual FRCs in terms of adherence that go beyond the class effects assessed in the present systematic review. Furthermore, the potential mechanisms of action for the observed beneficial effect of FRCs on adherence in T2DM could be assessed. With the emergence of more evidence in future, it may be possible to conduct meta-analyses stratified by the methodological differences that led to considerable methodological heterogeneity and precluded meta-analysis being conducted in the present systematic review.

5. Conclusions

This review demonstrates that FRCs, as a class of injectable medication used for diabetes treatment have major benefits in terms of patient outcomes. They can improve patient satisfaction with treatment, reduce treatment burdens and improve adherence, resulting in potentially improved glycaemic control in the process.

Competing interests

The authors have no competing interests to declare.

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Declaration of competing interest

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Appendix A. Supplementary data

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