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Short-Term Real-World Clinical Outcomes of the Fixed-Ratio Combination of Insulin Glargine and Lixisenatide in Type 2 Diabetes

Tip 2 Diyabette İnsülin Glarjin ve Liksisenatid Sabit Oranlı Kombinasyonunun Kısa Dönem Gerçek Yaşam Klinik Sonuçları

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ABSTRACT

Objective: To assess the short-term real-world effects of the fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) on glycemic control, body weight, insulin requirements, and the Fibrosis-4 (FIB-4) score in adults with type 2 diabetes mellitus (T2DM).

Methods: This retrospective study screened 122 adults initiated on iGlarLixi between January 1 and April 1, 2025. After excluding 40 patients who were receiving additional antidiabetic therapy and 12 who discontinued treatment due to intolerance or loss to follow-up, 70 patients were included in the final analysis. Body weight, body mass index, HbA1c, daily insulin dose, and FIB-4 were recorded at baseline and at 3 months. Paired t-tests or Wilcoxon signed-rank tests were used for continuous variables, and chi-square or Fisher's exact tests were used for categorical outcomes.

Results: Median age was 57 years, and 85.7% were female. Median baseline HbA1c was 9.05%, and the median FIB-4 was 0.91. At 3 months, weight decreased from 106.5 to 104 kg ($p < 0.001$), HbA1c decreased from 9.05% to 8.4% ($p < 0.001$), and insulin dose decreased from 27 to 24 U/day ($p < 0.001$). FIB-4 decreased modestly but significantly, from 0.91 to 0.85 ($p = 0.03$). In patients who added iGlarLixi to oral therapy, weight, HbA1c, and FIB-4 improved significantly (all $p < 0.03$). Among those switching from basal insulin to iGlarLixi, HbA1c and insulin dose decreased (both $p < 0.001$); weight change was minimal; and FIB-4 was unchanged ($p = 0.308$). Gastrointestinal adverse events occurred in 10% of cases; they were mild to moderate, and did not lead to discontinuation.

ÖZ

Amaç: Bu çalışmanın amacı, tip 2 diyabet mellituslu (T2DM) erişkinlerde insülin glarjin ve liksisenatid sabit oranlı kombinasyonunun (iGlarLixi) kısa dönem gerçek yaşam etkilerini; glisemik kontrol, vücut ağırlığı, insülin gereksinimi ve Fibrozis-4 (FIB-4) skoru üzerindeki değişimler açısından değerlendirmektir.

Yöntemler: Bu retrospektif çalışmada, 1 Ocak ile 1 Nisan 2025 tarihleri arasında iGlarLixi tedavisi başlanan 122 yetişkin hasta tarandı. Ek antidiyabetik tedavi alan 40 hasta ile intolerans veya takip kaybı nedeniyle tedaviyi bırakan 12 hastanın dışlanmasının ardından, 70 hasta nihai analize dahil edildi. Vücut ağırlığı, beden kitle indeksi, HbA1c, günlük insülin dozu ve FIB-4 değerleri başlangıçta ve 3. ayda kaydedildi. Sürekli değişkenler için eşleştirilmiş t-testi veya Wilcoxon işaretli sıralar testi, kategorik değişkenler için ki-kare veya Fisher kesin testi kullanıldı.

Bulgular: Medyan yaş 57 yıl olup hastaların %85,7'si kadındı. Medyan başlangıç HbA1c değeri %9,05 ve medyan FIB-4 skoru 0,91 idi. Üçüncü ayda vücut ağırlığı 106,5 kg'dan 104 kg'a ($p < 0,001$), HbA1c %9,05'ten %8,4'e ($p < 0,001$) ve günlük insülin dozu 27 U/gün'den 24 U/gün'e ($p < 0,001$) düştü. FIB-4 skoru da mütevazı ancak istatistiksel olarak anlamlı şekilde azaldı (0,91'den 0,85'e, $p = 0,03$). iGlarLixi'nin oral tedaviye eklendiği hastalarda vücut ağırlığı, HbA1c ve FIB-4 anlamlı olarak iyileşti (tümü $p < 0,03$). Bazal insülinden iGlarLixi'ye geçilen hastalarda HbA1c ve insülin dozu azaldı (her ikisi için $p < 0,001$), vücut ağırlığındaki değişim minimaldi ve FIB-4 değişmedi ($p = 0,308$). Gastrointestinal yan etkiler olguların %10'unda görüldü, hafif-orta şiddetteydi ve tedavinin kesilmesine yol açmadı.

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ABSTRACT

CONCLUSION: iGlarLixi improved glycemic control, reduced insulin requirements, and promoted weight loss in adults with poorly controlled T2DM. When added to oral antidiabetic therapy, iGlarLixi was also associated with a modest but significant reduction in FIB-4, suggesting potential benefits for the liver.

Keywords: Type 2 diabetes mellitus, insulin glargine/lixisenatide fixed-ratio combination, glycemic control, FIB-4 score, body weight

ÖZ

Sonuç: iGlarLixi, kötü kontrollü T2DM'li erişkinlerde glisemik kontrolü iyileştirmiş, insülin gereksinimini azaltmış ve kilo kaybını desteklemiştir. Oral antidiyabetik tedaviye eklendiğinde, iGlarLixi'nin FIB-4 skorunda da mütevazı ancak anlamlı bir azalma ile ilişkili olması, karaciğer açısından potansiyel faydalara işaret etmektedir.

Anahtar Sözcükler: Tip 2 diyabet mellitus, insülin glarjin/liksisenatid sabit oranlı kombinasyonu, glisemik kontrol, FIB-4 skoru, vücut ağırlığı

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by chronic hyperglycemia and insulin resistance, frequently accompanied by obesity and other cardiometabolic comorbidities (1,2). Despite advances in pharmacological treatment, maintaining adequate glycemic control remains difficult, especially in patients with long-standing disease who are already on basal insulin or multiple oral antidiabetic drugs (OADs) (3).

Obesity significantly contributes to the development and progression of T2DM, thereby making the achievement of optimal glycemic targets more challenging in affected individuals (4,5). Consequently, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as cornerstones in the management of both diabetes and obesity. These agents have consistently demonstrated efficacy in improving glycemic control, reducing body weight, and providing additional benefits for cardiovascular and liver (6). Moreover, fixed-ratio combinations of basal insulin and GLP-1 RAs, such as insulin glargine/lixisenatide, provide complementary mechanisms of action by simultaneously targeting fasting and postprandial glucose levels and mitigating insulin-associated weight gain. Their therapeutic effects are mediated through multiple pathways, including delayed gastric emptying, glucose-dependent modulation of insulin secretion, and central regulation of appetite. Although randomized trials have demonstrated their efficacy, real-world data on their impact on metabolic and liver parameters are limited (7,8).

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease. Therefore, preventing MASLD and detecting the risk of liver fibrosis (FIB) early are of critical clinical importance. To this end, clinicians frequently use various non-invasive assessment tools, including the fatty liver index, hepatic steatosis index, and the FIB-4 score (9). Notably, the FIB4 score is strongly recommended for monitoring patients with diabetes who are at risk of liver FIB. However, its responsiveness to fixed-ratio combinations of insulin and GLP-1 RAs therapies has not been thoroughly studied (10,11).

This study aimed to evaluate the effects of adding or switching to a fixed-ratio combination of insulin glargine/lixisenatide (iGlarLixi) on glycemic control, body weight, insulin requirements, and FIB-4 scores in patients with type 2 diabetes.

MATERIALS AND METHODS

Study Design and Participants

This retrospective observational study included adult patients (≥18 years) with T2DM who were initiated on iGlarLixi at our Endocrinology and Metabolism Clinic. A total of 70 patients meeting the inclusion criteria between January 1, 2025, and April 1, 2025, were enrolled.

Inclusion criteria were: (1) age ≥18 years, (2) diagnosis of T2DM according to the American Diabetes Association criteria (12), and (3) initiation of iGlarLixi. Exclusion criteria were: (1) addition of any new antidiabetic agents (oral or injectable) at the time of initiation or during the 3-month follow-up period; (2) insufficient baseline or follow-up data; and (3) discontinuation of therapy within the first 3 months due to adverse effects or other reasons.

Out of 122 screened patients, 40 were excluded for receiving additional antidiabetic therapy, and 12 discontinued treatment within the first 3 months due to intolerance or other reasons. Consequently, 70 patients were included in the final analysis. The process of patient selection is summarized in Figure 1.

Data Collection

Data on body weight (kg), body mass index [(BMI), kg/m²], glycated hemoglobin (HbA1c, %), daily total insulin dose (units), FIB-4, and other treatment-related adverse effects were collected at the baseline (month 0) and after 3 months (month 3). Adverse effects were recorded based on patient reports and medical records. The FIB-4 score was calculated using the following validated formula:

$$\text{FIB-4} = \frac{\text{Age [years]} \times \text{AST [U/L]}}{\text{Platelet count [}10^9\text{/L]} \times \sqrt{\text{ALT [U/L]}}}$$

where AST is aspartate aminotransferase and ALT is alanine aminotransferase (13).

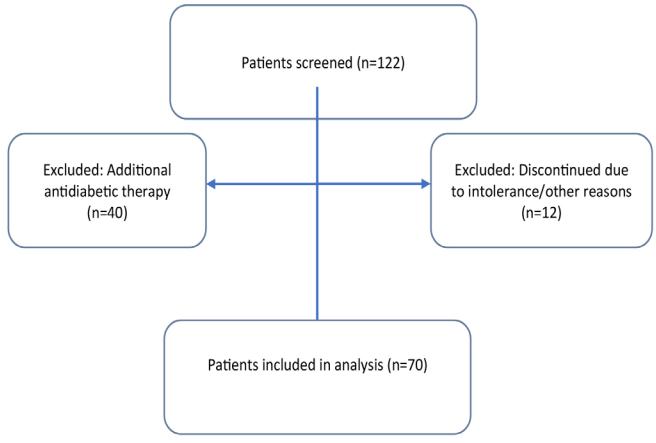


Figure 1. Patient flow chart.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR), depending on their distribution. Comparisons between baseline and 3-month values were performed using paired-sample t-tests or Wilcoxon signed-rank tests, as appropriate. Categorical variables, including hypoglycemic events and other adverse effects, were expressed as counts and percentages and were compared using the chi-square or Fisher's exact tests. The correlation between changes in FIB-4 and body weight over the 3-month period was assessed using Spearman's rank correlation coefficient (for non-normally distributed data). A p-value <0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics (version 27.0).

Ethical Considerations

All study procedures adhered to the Declaration of Helsinki, and ethical approval was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (approval number/date: AEŞH-BADEK2-2025-379/05-08-2025, dated 05.08.2025). Due to the retrospective nature of the study, the requirement for informed consent was waived.

RESULTS

Baseline Characteristics

A total of 70 patients were analyzed. The median age was 57 years (IQR: 51.4–62.7), and 85.7% were female. The median BMI and body weight were 41.95 kg/m² (IQR: 38.05–45.85) and 106.5 kg (IQR: 94–114.25), respectively. The median duration of diabetes was 12 years (IQR: 8.0–16.25), with a baseline HbA1c of 9.05% (IQR: 8.35–10.05). The baseline FIB-4 score was 0.91 (IQR: 0.65–1.09). The median total daily insulin dose was 27 units (IQR: 20–56.2). Gastrointestinal adverse events (GI AEs) were reported in 10% of patients. These baseline demographic and clinical characteristics are summarized in Table 1.

Overall Changes from Baseline to the Third Month

Changes in clinical and laboratory parameters from baseline to the third month of treatment are summarized in Table 2. There was a statistically significant reduction in body weight [median 106.5 kg (IQR: 94–114.25) vs. 104 kg (IQR: 93.75–113.25); p < 0.001] and HbA1c levels [median 9.05% (IQR: 8.35–10.05) vs. 8.4% (IQR: 7.3–9.0); p < 0.001]. The FIB-4 score also showed a modest but significant decrease [median 0.91 (IQR: 0.65–1.09) vs. 0.85 (IQR: 0.63–1.03); p = 0.03]. Additionally, the median total daily insulin dose decreased from 27 units (IQR: 20–56.2) to 24 units (IQR: 17.75–50) (p < 0.001). During the 3-month follow-up, 4 patients (5.1%) reported hypoglycemia; all episodes were mild.

Subgroup Analysis: Addition of iGlarLixi to OAD

The changes observed after adding iGlarLixi to ongoing OAD therapy are presented in Table 3. There was a significant reduction in body

Table 1. Baseline demographic and clinical characteristics of the study population.

Demographic and clinical variables	Median [IQR]/n (%)
Age (years)	57 [51.4–62.7]
Sex (female/male)	60 (85.7%) / 10 (14.3%)
BMI (kg/m²)	41.95 [38.05–45.85]
Body weight (kg)	106.5 [94–114.25]
Duration of diabetes (years)	12 [8.0–16.25]
HbA1c (%)	9.05 [8.35–10.05]
Baseline FIB-4 score	0.91 [0.65–1.09]
Total insulin dose (U/day)	27 [20–56.2]
Number of patients with GI AEs	7 (10%)
Hypoglycemia events, n (%)	4 (5.1%)

BMI: Body mass index, FIB-4: Fibrosis-4 score, GI AEs: Gastrointestinal adverse events, HbA1c: Glycated hemoglobin, IQR: Interquartile range.

Table 2. Comparison of clinical and laboratory parameters between baseline and the third month of treatment.

Parameter	Baseline median [IQR]	3rd month median [IQR]	p-value
Body weight (kg)	106.5 [94–114.25]	104 [93.75–113.25]	<0.001
HbA1c (%)	9.05 [8.35–10.05]	8.4 [7.3–9.0]	<0.001
FIB-4 score	0.91 [0.65–1.09]	0.85 [0.63–1.03]	0.030
Total insulin dose (U/day)	27 [20–56.2]	24 [17.75–50]	<0.001
Hypoglycemia events, n (%)	N/A	4 (5.1%)	N/A

FIB-4: Fibrosis-4 index, HbA1c: Glycated hemoglobin, N/A; Not available, IQR: Interquartile range.

Table 3. Changes in clinical and laboratory parameters after adding iGlarLixi to OAD.

Parameter	Baseline median [IQR]	3rd month median [IQR]	p-value
Body weight (kg)	104.5 [90.75–114.25]	102 [90.75–112.25]	0.005
HbA1c (%)	9.15 [8.17–9.9]	8.0 [7.2–9.0]	<0.001
FIB-4	0.92 [0.61–1.21]	0.84 [0.63–1.04]	0.030
Total insulin dose (U/day)	20 [14–21]	26 [18–34]	0.002

FIB-4: Fibrosis-4 score, HbA1c: Glycated hemoglobin, OAD: Oral antidiabetic drug, IQR: Interquartile range.

weight [median 104.5 kg (IQR: 90.75–114.25) vs. 102 kg (IQR: 90.75–112.25); p = 0.005] and HbA1c levels [median 9.15% (IQR: 8.17–9.9) vs. 8.0% (IQR: 7.2–9.0); p < 0.001]. The FIB4 score also decreased significantly [median 0.92 (IQR: 0.61–1.21) vs. 0.84 (IQR: 0.63–1.04); p = 0.03]. The baseline median insulin dose in this subgroup was 20 units/day (IQR: 14–21). Furthermore, the total daily insulin dose increased modestly during the 3-month follow-up [26 (IQR: 18–34); p = 0.002], reflecting treatment intensification and active dose titration to improve glycemic control.

Table 4 examines the correlation between changes in FIB-4 score and changes in body weight among patients on OADs with add-on iGlarLixi therapy. Spearman's rank analysis showed a weak, non-significant positive correlation between ΔFIB-4 and Δbody weight (ρ = 0.191, p = 0.312).

Subgroup Analysis: Switching from Insulin Glargine to iGlarLixi

Among patients who switched from insulin glargine to iGlarLixi, HbA1c [9% (IQR: 8.5–10.4) to 8.5% (IQR: 7.3–9.5); p < 0.001] and total daily insulin dose [50 units (IQR: 26–82) to 34 units (IQR: 20–64); p < 0.001] decreased significantly. Weight reduction was also statistically significant, but minimal [from 107 kg (IQR: 96–116) to 107 kg (IQR: 95–114); p < 0.001]. No significant change was observed in the FIB-4 score (p = 0.308; Table 5).

DISCUSSION

In this study, we evaluated the effects of iGlarLixi combination therapy on glycemic control, FIB-4 score, body weight, and insulin requirements in patients with T2DM. After three months of treatment, we observed significant reductions in HbA1c, body weight, and total daily insulin dose; these changes were accompanied by a modest but statistically significant decrease in FIB-4 in the overall cohort and were particularly evident among patients who received combination therapy in addition to OADs. Notably, patients who switched from insulin glargine to iGlarLixi achieved improved glycemic control with a substantially lower insulin requirement. These findings highlight the potential of combining basal insulin with a GLP-1 RA to enhance glycemic outcomes, reduce insulin need, and favorably impact surrogate markers of liver FIB in patients with long-standing, poorly controlled T2DM.

Table 4. Correlation between FIB-4 score changes and body weight in patients using OAD.

Variables	Spearman's ρ	p-value
ΔFIB-4 vs. Δbody weight	0.191	0.312

Δ: Change; FIB-4: Fibrosis-4 score, OAD: Oral antidiabetic drugs.

In the present study, switching from insulin glargine to iGlarLixi or adding iGlarLixi to OADs improved both glycemic control and weight management. In both groups, significant reductions in HbA1c level and weight were observed. These results are consistent with the existing literature (14,15). In a systematic review and meta-analysis comparing premixed and basal insulin with insulin glargine/lixisenatide, iGlarLixi was superior to premixed insulin and to basal-plus regimens in reducing HbA1c and managing weight. Furthermore, the basal bolus regimen had a similar effect on HbA1c as the insulin glargine/lixisenatide combination (14). In addition, Goldman and Trujillo (16) demonstrated that combination therapy with insulin glargine and lixisenatide resulted in a greater reduction in HbA1c compared with either glargine or lixisenatide alone. Notably, despite this enhanced glycemic effect, the incidence of hypoglycemic events was lower than with monotherapies (16). The combination therapy allows the use of lower doses of both insulin and lixisenatide, thereby reducing the risk of hypoglycemia, improving glycemic control, and exerting a neutral or more favorable effect on weight management. These benefits are attributable to the GLP-1 receptor–mediated mechanisms, including delayed gastric emptying, inhibition of glucagon secretion, and glucose-dependent stimulation of insulin release(17,18).

We demonstrated that switching from insulin glargine to iGlarLixi resulted in a lower total insulin dose. Although 10% of patients experienced dyspeptic symptoms, no patients discontinued treatment because of these adverse effects. These findings are consistent with previous reports (19,20). In the LixiLanL trial, GI AEs were reported in 17% of patients, mostly mild to moderate symptoms such as nausea, vomiting, or diarrhea (19). Importantly, as in our cohort, no patients in that study discontinued treatment due to GI AEs. Severe adverse events, including pancreatitis, were not observed during the three-month follow-up period. Likewise, phase 3 LixiLan trials reported no episodes of pancreatitis, with an overall very low incidence (19,20). Several studies have also shown that improved glycemic control in both premixed and basalbolus regimens can be achieved with lower total insulin doses, consistent with our results (19-22). This effect is attributable to the actions of GLP-1 RAs, which slow gastric emptying, suppress appetite centrally, and enhance glucose-dependent insulin secretion (23,24). Moreover, the use of a lower insulin dose provides additional benefits, including reduced weight gain, fewer injections, and improved quality of life (25,26).

The FIB-4 score is commonly used to assess the risk of hepatic FIB in patients with T2DM. Furthermore, the ADA recommends screening all patients with T2DM for MASLD. If the FIB-4 score is higher than 1.3, this patient should be referred to a gastroenterologist (10). Treatment options for slowing or improving liver FIB are limited,

Table 5. Changes in clinical and laboratory parameters after switching from insulin glargine to iGlarLixi.

Parameter	Baseline median [IQR]	3rd month median [IQR]	p-value
Body weight (kg)	107 [96–116]	106 [95–114]	<0.001
HbA1c (%)	9 [8.5–10.4]	8.5 [7.3–9.5]	<0.001
FIB-4	0.91 [0.65–1.09]	0.85 [0.63–1.03]	0.308
Total insulin dose (U/day)	50 [26–82]	34 [20–64]	<0.001

FIB-4: Fibrosis-4 score, HbA1c: Glycated hemoglobin, IQR: Interquartile range.

and GLP-1 RAs are among the few available options (27,28). In a study evaluating the effect of lixisenatide on non-alcoholic fatty liver disease in T2DM, the aspartate aminotransferase-to platelet count ratio was used to assess liver FIB. Lixisenatide led to improvements in liver inflammation and FIB (29). These findings are consistent with our research. In contrast, a systematic review reported that lixisenatide normalized ALT levels but had no significant effect on AST, alkaline phosphatase, or bilirubin (30). Furthermore, our findings indicate that this effect is independent of weight loss. An improvement in the FIB4 score was observed in the group receiving OAD. In this group, withdrawal of some OADs upon initiation of iGlarLixi therapy may have contributed to the observed improvement in liver enzymes. Importantly, the short-term changes observed in FIB-4 should be interpreted with caution, as they may partly reflect medication adjustments and metabolic improvements rather than true regression of liver FIB. Given the relatively short follow-up period, variations in FIB-4 may primarily reflect dynamic changes in the biochemical parameters comprising the score. Therefore, prospective studies with longer follow-up periods and histological or imaging-based assessments are warranted to better clarify the independent effects of iGlarLixi on liver FIB.

This study has several strengths, including its use of a real-world cohort of patients with long-standing, poorly controlled T2DM and a high BMI, thereby enhancing the clinical relevance of the findings. The comprehensive evaluation of glycemic control, insulin requirements, body weight, and FIB-4 scores provided a multidimensional assessment of treatment effects. However, the three-month follow-up period limits the ability to draw conclusions about long-term efficacy and safety. The modest sample size, particularly in subgroup analyses, may have reduced statistical power. Additionally, relying solely on the FIB-4 score may not fully capture changes in hepatic status. The observed reduction in FIB-4 warrants cautious interpretation because this surrogate index is influenced by biochemical parameters; short-term changes may primarily reflect variations in liver enzyme levels rather than true regression of hepatic FIB. Finally, because this was a single-center study, the results may not be generalizable to all patient populations.

CONCLUSION

iGlarLixi resulted in significant improvements in glycemic control, body weight, and total daily insulin requirements in patients with long-standing T2DM. A modest yet statistically significant reduction in FIB4 scores was observed in the subgroup receiving the combination alongside oral antidiabetic therapy. These results underscore the potential of combining basal insulin with a GLP-1 RA to enhance both metabolic control and a surrogate marker of hepatic status in real-world clinical practice. Further comprehensive, long-term studies are needed to confirm these findings and clarify their clinical implications.

Ethics

Ethics Committee Approval: All study procedures adhered to the Declaration of Helsinki, and ethical approval was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (approval number/date: AEŞH-BADEK2-2025-379/05-08-2025, dated 05.08.2025).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ü., B.Ç.H., Concept: E.Ü., B.Ç.H., B.U., Design: E.Ü., B.M., B.U., E.Ç., Data Collection or Processing: E.Ü., B.M., Analysis or Interpretation: E.Ü., Literature Search: E.Ü., B.Ç.H., Writing: E.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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