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Comparative effectiveness of immediate-release and extended-release metformin on gastrointestinal tolerability, quality of life, and treatment satisfaction

A prospective cohort study

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Abstract

Gastrointestinal (GI) side effects from metformin often limit its use and can impact patient quality of life (QoL) and satisfaction. The extended-release (XR) formulation is thought to cause fewer GI adverse events than immediate-release (IR) metformin, potentially improving tolerability, treatment satisfaction, and adherence. To compare metformin IR vs XR in terms of GI tolerability (incidence of GI side effects), patient-reported QoL, and medication satisfaction over 6 months in Saudi patients with type 2 diabetes. In a prospective cohort of 119 newly diagnosed patients with type 2 diabetes (62 on IR, 57 on XR), we tracked GI adverse events using a standardized questionnaire at baseline and 6-month follow-up. Diabetes-specific QoL was measured with the diabetes therapy-related quality of life questionnaire (DTR-QOL), and treatment satisfaction was assessed with the oral hypoglycemic agent questionnaire version 2 (OHA-Q ver. 2). Metformin XR was associated with significantly better GI tolerability. By 6 months, 45.2% of IR patients and only 24.5% of XR patients reported any GI side effect (P <.05). Rates of bothersome symptoms, such as diarrhea, were notably higher in the IR group. Patients on XR reported fewer interruptions of therapy due to GI upset. The DTR-QOL global score improved in both groups (P <.05), but there was no significant difference in total DTR-QOL scores between groups (P = .390). The OHA-Q ver. 2 global score improved in both groups (P <.05), but the XR group had higher scores in domains related to satisfaction (median treatment satisfaction domain score 100 vs 77.78 for IR, P < .05), with a significant difference in OHA-Q ver. 2 global score (92.59 vs 86.31 for IR; P <.05). Metformin XR demonstrated superior GI tolerability, which translated into improved treatment satisfaction compared to IR. While the overall quality of life related to diabetes management improved similarly with both, the XR formulation reduced side effect burden, and the lower daily dosing led to higher patient-reported satisfaction. These findings support the use of metformin XR to enhance tolerability and adherence, potentially leading to improved long-term outcomes.

Abbreviations: ADT = anxiety and dissatisfaction with treatment (DTR-QOL domain), BSDA = Burden on social and daily activities (DTR-QOL domain), DTR-QOL = diabetes therapy-related quality of life questionnaire, GI = gastrointestinal, HG = hypoglycemia (DTR-QOL domain), IR = immediate-release (metformin), OHA-Q = oral hypoglycemic agent questionnaire, OHA-Q ver. 2 = oral hypoglycemic agent questionnaire version 2, QoL = quality of life, RCT = randomized controlled trial, SF = satisfaction (OHA-Q ver. 2 subscale), SS = somatic symptoms (OHA-Q ver. 2 subscale), ST = satisfaction with treatment (DTR-QOL domain), T2DM = type 2 diabetes mellitus, TC = treatment convenience (OHA-Q ver. 2 subscale), XR = extended-release (metformin).

Keywords: gastrointestinal side effects, metformin extended-release, metformin immediate-release, quality of life, treatment satisfaction, type 2 diabetes

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study protocol received approval from the relevant ethical committees: the Local Research Ethics Committee at the University of Tabuk, Saudi Arabia (Approval No. UT-190-46-2022; 16th March 2022), the Tabuk Institutional Review Board of the Ministry of Health, Saudi Arabia (Protocol No. TU-077/022/137; 31st May 2022), and the Ethics Committee for Research Involving Human Subjects at Universiti Putra Malaysia (Reference No. JKEUPM-2022-860; 7th March 2023). Participants provided additional consent to answer the questionnaires, understanding that their responses would be kept confidential and used solely for research purposes. All procedures (interviews and surveys) were conducted in a manner that respected patient privacy. The data presented herein do not contain any identifying information and have been aggregated to ensure anonymity.

The study was conducted independently, with no involvement from or support provided by pharmaceutical companies. The conclusions drawn are solely based on the data collected and are free of any commercial bias.

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1. Introduction

Type 2 diabetes mellitus (T2DM) remains a major global health challenge, with particularly high burden in the Middle East. In Saudi Arabia, recent estimates suggest prevalence rates ranging from 16% to over 20%.[1–3] The Kingdom rapid urbanization, lifestyle shifts, and rising obesity rates are likely driving this trend.[4] T2DM is pathophysiologically defined by insulin resistance; metformin, a biguanide that enhances insulin sensitivity, continues to be the guideline-recommended first-line therapy due to its glycemic efficacy, weight-neutral profile, and favorable cardiovascular outcomes.[5,6]

The use of metformin is often hindered by gastrointestinal (GI) adverse effects. In large observational series, GI symptoms, including diarrhea, nausea, abdominal discomfort, and bloating, occur in up to 20% to 30% of users, and around 5% discontinue therapy due to intolerance.[7,8] These side effects may erode patients' quality of life (QoL) and adherence, undermining the very benefits metformin is intended to deliver.

To mitigate this challenge, metformin is available in immediate-release (IR) and XR formulations. The XR formulation was engineered to attenuate peak intestinal concentrations, thereby reducing GI irritation, while enabling once-daily dosing that simplifies the regimen and potentially enhances adherence.[9] Clinical adoption of XR, especially in patients intolerant to IR, is already common in practice, yet robust comparative data remain limited.[7]

Given that patient-centered outcomes, including treatment satisfaction (TS), QoL, and adherence, are increasingly recognized as critical to long-term diabetes management, it is imperative to assess how formulation influences them. Evidence suggests that better adherence correlates with improved QoL in T2DM, driven by fewer side effects and simpler regimens.[8,10] If XR can convincingly reduce GI toxicity, one would expect improvements in QoL domains associated with treatment burden.

Some randomized and observational studies have suggested that XR may have advantages. For example, a 2021 RCT in China found that XR and IR had comparable efficacy but with fewer GI side effects in the XR arm.[9] Other meta-analyses and retrospective reports suggest that XR is associated with improved tolerability compared to IR.[11] However, how these tolerability gains translate into real-world patient-reported outcomes, such as quality of life (QoL) and satisfaction, has not been fully explored in Saudi populations.

Our study aims to compare metformin IR and XR in terms of GI tolerability (frequency of GI side effects), diabetes-related quality of life, and TS in a Saudi patient population. We hypothesize that the extended-release (XR) metformin will result in fewer GI side effects, leading to higher TS compared to IR metformin. However, overall diabetes QoL improvement might be similar once glycemic control is achieved. By focusing on these patient-centered outcomes, we aim to provide evidence that extends beyond glycemic numbers to encompass considerations of patient comfort and treatment acceptance.

2. Materials and methods

2.1. Study design

A prospective cohort study design was employed to compare outcomes between 2 groups of patients with type 2 diabetes: those receiving metformin IR and those receiving metformin XR. The study was observational in nature (nonrandomized), aligning with real-world prescribing: patients were already receiving either IR or XR metformin as part of their initial diabetes management. Outcomes were assessed at baseline (study entry) and after 6 months of follow-up on therapy. This design allowed for the evaluation of changes over time within each group and comparisons between the 2 groups.

2.2. Study location and duration

The study was conducted at the Diabetes Center of King Fahad Specialist Hospital in Tabuk, Saudi Arabia. This center is a major referral clinic providing comprehensive diabetes care for the region. The recruitment and follow-up took place between March 2023 and December 2024. Baseline data collection commenced in March 2023, and the final 6-month follow-up assessments were completed by the end of 2024, resulting in an approximately 21-month enrollment period to accrue the cohort and observe each patient for 6 months.

2.3. Study population

The target population was adults in Tabuk region with newly diagnosed type 2 diabetes who were started on metformin as first-line therapy. The study specifically involved patients who had been prescribed either metformin IR or metformin XR (as monotherapy) as part of their routine diabetes treatment. All participants were Saudi nationals, reflecting the local patient demographics of the hospital's catchment area.

2.4. Inclusion and exclusion criteria

The inclusion criteria were as follows: Age 18 years or older; newly diagnosed T2DM (diagnosed within the past 3 months) with no prior antidiabetic pharmacotherapy before metformin; currently prescribed metformin IR or metformin XR as the sole glucose-lowering medication; and willing and able to give informed consent and comply with study procedures (including attending follow-up visits and completing questionnaires). Both male and female patients were eligible for participation.

The exclusion criteria were as follows: Patients with type 1 diabetes or other forms of diabetes (e.g. gestational diabetes); use of any other oral hypoglycemic agents or insulin at baseline; a history of significant gastrointestinal disorders or surgeries that could independently affect GI symptoms (such as peptic ulcer disease, inflammatory bowel disease, or gastric bypass surgery); any contraindication to metformin (such as renal insufficiency with eGFR below the metformin safety threshold, or severe hepatic impairment); pregnant or lactating women (metformin can be used in pregnancy for certain cases, but such patients were beyond our scope and pregnancy itself could affect QoL independently); patients who had used antibiotics, proton pump inhibitors, or other medications known to influence gastrointestinal function within the past 3 months; and inability to complete the questionnaires due to cognitive, visual, or language barriers.

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2.5. Sample size

The sample size was determined based on the ability to detect a meaningful difference in TS (a patient-reported outcome) between the IR and XR groups at 6 months. Using a 2-sided test with $\alpha = 0.05$ and a power of 80%, we estimated that approximately 50 to 60 patients per group would be required to detect a moderate effect size in satisfaction scores. Anticipating some loss to follow-up or withdrawals, we aimed to recruit a total of approximately 140 patients. Ultimately, 142 eligible patients were enrolled at baseline. By the 6-month follow-up, 119 patients remained in the study with complete data (62 in the metformin IR cohort and 57 in the metformin XR cohort). This final sample size provided slightly more than the minimum power required, allowing for robust comparisons between groups.

2.6. Sampling technique

A systematic random sampling approach was employed to enroll participants from the center. Newly diagnosed T2DM patients who met the inclusion criteria were identified from the center records and approached sequentially. To reduce selection bias, we used a system in which every nth eligible patient (for example, every second patient) presenting to the Diabetes Center was invited to participate, starting from a random point. This systematic sampling continued throughout the recruitment period. All patients who were invited and gave consent were enrolled until the target sample size was reached. Patients were assigned to the IR or XR group based on the formulation of metformin prescribed by their treating physicians (the study did not dictate treatment allocation; it observed the existing prescription practice). We tracked the number of patients who declined participation and found it to be minimal, yielding a high response rate.

2.7. Data collection

Data were collected at 2 main points: baseline (at the time of enrollment, shortly after metformin initiation) and at the 6-month follow-up visit. At baseline, after obtaining written informed consent, each participant underwent an interview and assessment to gather demographic and clinical information. We used a structured data collection report titled "Socio-demographic, Body Measurements, Laboratory Parameters, and GI Adverse Events Report (SBLG-R)." This form captured socio-demographic data (age, sex, etc), medical history, and baseline clinical measurements. It also included an inventory of any gastrointestinal symptoms experienced since starting metformin (capturing the presence of side effects like nausea, bloating, diarrhea, etc, at baseline). Baseline metabolic parameters were obtained, including body measurements (weight and height for calculating BMI) and laboratory tests: fasting blood glucose, glycated hemoglobin (HbA1c), fasting insulin, and lipid profile (total cholesterol, triglycerides, HDL-C, and LDL-C). These measurements were taken for another project, which was part of a comprehensive work.

2.7.1. Two questionnaires were administered to assess patient-reported outcomes.

- **The Diabetes Therapy-Related Quality of Life Questionnaire (DTR-QOL):** This is a validated diabetes-specific QoL instrument focused on the impact of therapy. It contains multiple domains: e.g., "burden on social and daily activities (BSDA)," "anxiety and dissatisfaction with treatment (ADT)," "hypoglycemia (HG)," and "satisfaction with treatment (ST)," among others, as well as a global QoL score. We used the DTR-QOL questionnaire, which was piloted and then validated after translation into Arabic as a part of this study.[12] The translation process involved forward translation, expert panel review, back translation, and pilot testing to ensure clarity and cultural appropriateness. The final Arabic version demonstrated good internal consistency (Cronbach α for the overall questionnaire was >0.9 in our pilot) and content validity.
- **The Oral Hypoglycemic Agent Questionnaire version 2 (OHA-Q ver. 2):** This tool is specifically designed to measure satisfaction and acceptance of oral diabetes medications. It includes subscales for treatment convenience (TC, the ease and simplicity of the regimen), TS (overall contentment with the medication's effects and use), and symptom burden or somatic symptoms (SS, the extent of side effects experienced). The OHA-Q was also translated into Arabic and validated similarly to the DTR-QOL.[13] It was administered by interview at 6 months to minimize any issues with literacy and to ensure completeness.

Both questionnaires were completed through face-to-face interviews at baseline (reflecting their initial experiences or expectations with their new metformin therapy) and again at 6 months (reflecting the last few weeks of their treatment experience).

Throughout the 6-month period, patients continued their prescribed metformin regimen. They received standard diabetes education and lifestyle advice from the Diabetes Center, and any medication adjustments were noted. We asked patients to report whether they had switched formulations or stopped taking metformin; however, according to the study protocol, we aimed to analyze them in their original group (intention-to-treat approach), while noting any crossover.

At the 6-month follow-up visit, the assessments were repeated. GI adverse events in the past month were recorded using the same SBLG-R form section for GI events, focusing on whether participants experienced specific symptoms (such as diarrhea, nausea, etc).

All data were entered into a secure database. Questionnaire scores (DTR-QOL domain scores and OHA-Q ver. 2 subscale scores) were calculated according to their scoring manuals (with necessary reverse coding or conversions). The research team performing data collection was trained in administering the interviews and questionnaires to ensure consistency and accuracy.

2.8. Measures

GI tolerability was assessed through structured patient interviews at baseline (~2 weeks after starting metformin to capture initial side effects) and at the 6-month visit. We used a questionnaire section (part of the SBLG-R form) listing common GI adverse events: abdominal pain, abdominal bloating, nausea, vomiting, diarrhea, and constipation. Patients were asked whether they experienced each symptom within the first 2 weeks of starting metformin (baseline report) and within the last 4 weeks of the 6-month follow-up period. We also computed a composite "any GI side effect" incidence rate for each group at baseline and follow-up.

Quality of life: Measured by the DTR-QOL questionnaire. The primary QoL outcome was the change in the global DTR-QOL score from baseline to 6 months in each group, and the difference in 6-month global QoL between the IR and XR groups. The DTR-QOL global score ranges from 0 to 100, with higher scores indicating better quality of life related to diabetes therapy. We also examined the 4 main DTR-QOL domains: BSDA, ADT, HG, and ST (each scored 0–100). Of particular interest were the "Burden on Social/Daily Activities" domain and the "ST" domain, as these were hypothesized to improve more with XR (due to fewer side effects and easier dosing). The HG (hypoglycemia) domain was expected to be high in both groups, as metformin does not typically cause hypoglycemia; this served as a control domain to confirm that differences in

QoL were specifically related to TC and side effects, rather than glycemic efficacy.

Treatment satisfaction: Measured by the OHA-Q ver. 2 questionnaire. The primary satisfaction outcome was the change in the global OHA-Q ver. 2 score from baseline to 6 months in each group, as well as the difference in 6-month global satisfaction between the IR and XR groups. The OHA-Q ver. 2 global score ranges from 0 to 100, with higher scores indicating greater satisfaction with diabetes therapy. We also examined the 4 main OHA-Q ver. 2 subscales (each scored 0–100), such as TC and concerns about side effects or blood glucose (SS and SF subscales, where SS refers to SS and SF is satisfaction or a similar concept, as per the references).

2.9. Data analysis

Data analysis was performed using IBM SPSS Statistics (Version 29.0.2.0, Chicago). We first conducted descriptive statistics. Continuous variables are presented as mean ± standard deviation if normally distributed, or median (interquartile range) if skewed. Categorical variables are presented as frequencies and percentages.

Baseline characteristics of the IR and XR groups were compared to assess any initial differences. For continuous variables, we used an independent-sample *t*-test (or the Mann–Whitney *U* test if the data were not normally distributed). For categorical variables, we used Chi-square tests. This was important to ensure the groups were comparable at baseline.

For GI side effects, we compared incidence rates between the IR and XR groups using a chi-square test. For the global GI symptom score, which is continuous, we used the Mann–Whitney *U* test to compare median scores between IR and XR at 6 months. We also compared the baseline versus 6-month incidence within each group (using Chi-square, McNemar, and Friedman tests for paired proportions) to determine if GI side effects subsided over time. A paired sample t-test for continuous parametric global score was used to examine the within-group change from baseline to 6 months, and the Wilcoxon signed-rank test was used for continuous nonparametric global score.

DTR-QOL and OHA-Q ver. 2 scores were approximately continuous and were compared between groups at follow-up using the Mann–Whitney *U* test, as the data were not normally distributed. Within-group changes in DTR-QOL and OHA-Q ver. 2 scores from baseline to 6 months were assessed using a paired sample *t*-test for parametric data, and the Wilcoxon signed-rank test was used for nonparametric data.

Results are presented with appropriate 95% confidence intervals where applicable, especially for key differences. All graphs were generated to visualize findings, and a 2-tailed *P*-value <.05 was considered statistically significant for all comparisons.

3. Results

Baseline characteristics: A total of 119 patients completed the study (62 in the metformin IR group and 57 in the metformin XR group). The 2 groups were well-matched in baseline demographic and clinical characteristics. The overall mean age was 50.3 ± 8.7 years, and 47.1% of the participants were male. There were no significant differences between the IR and XR cohorts in age, gender distribution, or duration of diabetes at baseline.

GI tolerability: At baseline (roughly 2 weeks into therapy), the incidence of any GI adverse event was high in both groups but somewhat higher in the XR group. 54.8% of patients on metformin IR reported at least one GI symptom in the first 2 weeks, compared to 77.1% of those on metformin XR (the XR group's initial incidence was slightly higher, possibly due to initial titration; this difference was not statistically significant). The global GI score was comparable between the 2 groups (*P* = .607). The most common baseline symptoms were abdominal bloating (~23% IR vs ~19% XR) and mild nausea (~13% IR vs ~19% XR). Notably, this baseline captures initial intolerance, as XR was administered at a roughly equivalent dose (750 mg BID = 1500 mg) to IR (500 mg TID = 1500 mg); therefore, it appears that initial GI effects were fairly similar or even slightly more pronounced in the XR group at the very start. This may be because XR tablets were started at a higher single dose (750 mg at once), which can still cause initial upset in some patients.

However, by the 6-month follow-up, the prevalence of GI side effects diverged markedly between the groups. Figure 1 illustrates the incidence of specific GI side effects in each group at 6 months. After 6 months, 54.8% of IR group patients were free of GI side effects, indicating that 45.2% still experienced some ongoing or intermittent GI issues. In contrast, 75.5% of XR group patients reported no GI side effects (only 24.5% experienced any symptoms). In other words, the proportion of patients experiencing GI problems was significantly lower with XR (24.5%) compared to IR (45.2%) at follow-up. This indicates a substantial improvement in tolerability for XR.

Looking at specific symptoms after 6 months (Fig. 1): **Diarrhea:** 4.8% of IR patients versus 0% of XR patients reported episodes of diarrhea in the preceding month. With IR, diarrhea was a persistent nuisance in some patients, whereas it was absent in the XR group. **Abdominal bloating:** Remained the most common symptom in both groups, but less so with XR. 21.0% IR versus 10.5% XR reported frequent bloating. **Abdominal pain:** 11.3% IR versus 7.0% XR (not a significant difference). **Nausea:** Interestingly, 3.2% of the IR group versus 7.0% of the XR group reported nausea at 6 months. This was a small number of patients; the difference is not statistically significant. **Vomiting:** None in XR or IR had occasional vomiting episodes. **Constipation:** 4.8% IR versus 0% XR. Not significant, but note XR patients did not report constipation, whereas a few IR did, possibly due to dehydration from diarrhea or other issues.

The total GI adverse event burden (some patients had multiple symptoms) can be summarized by a "global GI score." The mean/median GI symptom global score decreased from baseline to 6 months in both groups, but more so in the XR group. For IR, the mean went from ~21.8 at baseline to 15.9 at 6 months (paired t = 2.48, *P* = .016, indicating a modest improvement after initial acclimation). For XR, the median decreased from 25 at baseline to ~8 at 6 months (a significant drop, *P* <.001). At 6 months, the between-group difference in median GI global score was statistically significant (*P* = .029), with lower GI side effects observed in the XR group. This indicates superior GI tolerability with XR, not only in terms of binary incidence, but also in overall symptom burden.

Quality of life (DTR-QOL): Baseline DTR-QOL scores were similar between groups. The global DTR-QOL score at baseline was around 67 in IR versus 78 in XR (out of 100), with no significant differences (reflecting that newly diagnosed patients have some QoL impact from disease and new treatment). Over 6 months, QOL improved in both cohorts, likely due to improved glycemic control and adaptation to diabetes, without any differences between groups, as shown in Table 1.

3.1. However, upon examining the specific domains of the DTR-QOL:

- **BSDA:** This domain evaluates the degree to which the treatment affects daily life. At 6 months, the XR group scored higher (better) on BSDA (median ~94) than the IR group (~91). The IR group improved from baseline (~78 to 91, *P* <.05 within group), and the XR improved from ~90

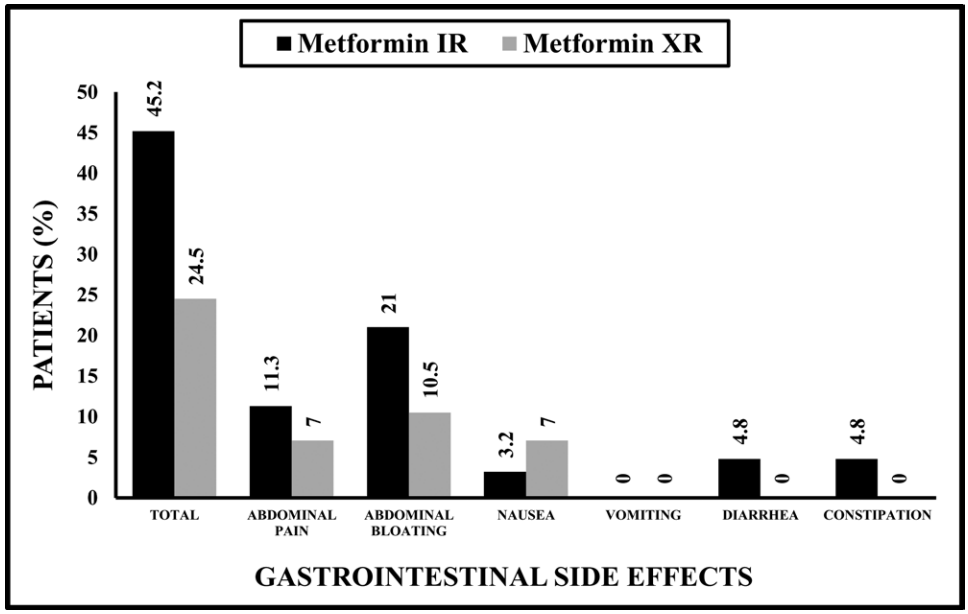

Figure 1. Incidence of gastrointestinal side effects at 6 mo in patients on metformin IR versus XR. The XR formulation had a markedly lower frequency of adverse GI symptoms. Notably, only 24.5% of XR patients experienced any GI side effect, compared to 45.2% of IR patients (P <.05). Individual symptoms such as abdominal pain and bloating were significantly more common in the IR group, while some symptoms (vomiting, diarrhea, and constipation) were absent in XR patients. GI = gastrointestinal, IR = immediate-release, XR = extended-release.

to ~94 (P <.001). The between-group difference in BSDA at follow-up was not significant (P = .278). This suggests both groups had the same burden of treatment in daily activities.

- **ADT:** This domain captures worries or unhappiness regarding treatment. Both groups showed reductions in ADT scores (indicating less anxiety) over time, with XR improving from ~80 to ~90, and IR from ~73 to ~80 as well (in fact, identical medians at follow-up, 90 for XR vs ~80 for IR, P = .007). So, in terms of general anxiety about treatment, both ended up similar. The initial improvement was significant in both (likely as patients got used to metformin and saw benefits).
- **Hypoglycemia (HG):** Both groups achieved perfect or near-perfect scores in the HG domain by 6 months (~100), as metformin doesn't cause hypoglycemia, and both likely realized this over time. There was no difference (no patient reported any hypo-related concerns in either group).
- **ST:** At baseline, many patients reported low satisfaction due to initial side effects and concerns about being on medication. By 6 months, this domain had improved dramatically in both groups (the IR group median increased from 75 to 100, and the XR mean rose from ~71 to ~77 on a 0–100 scale). Notably, the XR group had a median of ~88, whereas the IR group had a median of 100, with no significant difference (P = .226). This suggests that most patients in both groups became increasingly satisfied as their diabetes came under control.

The **global DTR-QOL score** significantly improved in both groups (IR from ~67 to ~85, XR from ~78 to ~88). XR group's global DTR-QOL at follow-up was slightly higher (~88 vs ~85, P = .390), but these improvements did not reach the statistical difference. So, the overall quality of life related to therapy was high in both groups. It appears that improvements were mostly in how convenient or burdensome the treatment felt.

Treatment satisfaction (OHA-Q ver. 2): Baseline OHA-Q ver. 2 scores were similar between groups. The global OHA-Q ver. 2 score at baseline was around 72 (out of 100) in both IR and XR groups, with no significant differences (reflecting that newly diagnosed patients have some satisfaction impact from the new treatment). Over 6 months, satisfaction improved in both cohorts; however, XR patients ultimately reported significantly higher levels of satisfaction. Key results from OHA-Q ver. 2 subscales are presented in Table 2.

Table 1

DTR-QOL scores of patients on metformin IR versus XR after 6 mo.

	Metformin IR, N = 62	Metformin XR, N = 57	
Variable/domain	**Median (IQR)**	**Median (IQR)**	***P*-value**
BSDA	91.03 (24.36)	93.59 (5.13)	.278
ADT	80.21 (39.58)	89.58 (18.75)	.007
HG	100.00 (8.33)	100.00 (6.25)	.609
ST	100.00 (20.83)	87.50 (50.00)	.226
Global DTR-QOL score	84.74 (22.52)	87.50 (17.15)	.390

Significant level at P <.05.

The Mann–Whitney U test was used in this statistical analysis for nonparametric data, with the median and IQR reported.

ADT = anxiety and dissatisfaction with treatment, BSDA = burden on social and daily activities, DTR-QOL = diabetes therapy-related quality of life questionnaire, HG = hypoglycemia, IQR = interquartile range, ST = satisfaction with treatment, XR = extended-release.

3.2. Looking at specific OHA-Q ver. 2 subscales, more apparent differences emerge:

- **TC subscale:** At 6 months, the TC subscale was similar between groups. The between-group difference in TC at follow-up was not significant (P = .615). However, each group reported significant improvement after therapy. The IR group improved from baseline (~74 to 94, P = .001 within group), and the XR improved from ~81 to ~96 (P <.001).
- **SS subscale:** This subscale measures the perceived burden of side effects (often scored such that a higher value means fewer or less bothersome symptoms). In our results, the within-group changes showed better improvements in this subscale for both groups (P = .002 for the IR group and P <.001 for the XR group). In the between-group comparison, the XR group scored significantly better, indicating

Table 2

OHA-Q versus 2 scores of patients on metformin IR versus XR after 6 mo.

	Metformin IR, N = 62	Metformin XR, N = 57	
Variable/subscale	**Median (IQR)**	**Median (IQR)**	***P*-value**
TC	94.44 (12.04)	96.30 (14.81)	.615
SS	78.79 (34.09)	90.91 (12.12)	.004
SF	77.78 (44.44)	100.00 (22.22)	.001
Global OHA-Q ver. 2 score	86.31 (26.94)	92.59 (7.63)	.003

Significant level at $P < .05$.

The Mann–Whitney *U* test was used in this statistical analysis for nonparametric data, with the median and IQR reported.

IQR = interquartile range, IR = immediate-release, OHA-Q ver. 2 = oral hypoglycemic agent questionnaire version 2, SF = satisfaction, SS = somatic symptom, TC = treatment convenience, XR = extended-release.

fewer side effects. The XR group's median was ~91, versus 79 in the IR group ($P = .004$). Practically, this means that XR patients reported "rarely" being bothered by any side effects, whereas IR patients, on average, reported being bothered between "rarely" and "sometimes." This aligns well with the GI symptom data; fewer XR patients had persistent side effects that bothered them. The difference is statistically significant and clinically meaningful, as it implies that significantly more IR patients found side effects to be a non-negligible issue.

- **SF subscale:** By 6 months, this subscale had improved in both groups (the IR group mean increased from ~69 to ~79, and the XR median rose from ~78 to 100 on a 0–100 scale). Notably, the XR group had a significantly higher median of 100, compared to the IR group, which had a median of ~78 ($P = .001$). This suggests that most patients in the XR group became more satisfied with their treatment than those in the IR group.

The global OHA-Q ver. 2 score significantly improved in both groups (IR from ~70 to ~82, XR from ~72 to ~93). XR group's global OHA-Q ver. 2 at follow-up was significantly higher (~93 vs ~86, $P = .003$).

In summary, metformin XR not only reduced the incidence of side effects but also enhanced patient satisfaction and adherence. These patient-centered improvements suggest that XR could lead to better long-term outcomes simply because patients take it more reliably and are happier with their therapy.

4. Discussion

Our comparative evaluation of metformin IR versus XR from the patient's perspective confirms several anticipated benefits of the XR formulation. The XR formulation was significantly better tolerated gastrointestinally compared to the IR formulation, and this improvement in tolerability had downstream positive effects on TS.

GI tolerability: By the 6-month follow-up, only 24.5% of patients on XR experienced any GI side effects, compared to 45.2% in the IR group, representing a nearly twofold higher incidence with IR. This supports the notion that the XR formulation's pharmacokinetics reduce the GI side-effect burden by avoiding high local drug concentrations in the intestines.[8,9,14] Pharmacodynamically, metformin impacts several gut-related pathways that contribute to GI side effects. It enhances intestinal glucose uptake and anaerobic metabolism, resulting in lactate accumulation in enterocytes. It also affects bile acid reabsorption, raises GLP-1 levels, and changes the gut microbiota composition. Although these effects help regulate blood glucose, they can also cause GI symptoms.[15–17] It is noteworthy that GI symptoms were common in both groups during the initial weeks of therapy (over half of patients in each group), which is higher than the ~20% to 30% rate of chronic metformin GI intolerance reported in the literature.[8,17] This likely reflects transient side effects that occur during metformin initiation and tend to improve over time. Indeed, as patients continued therapy, those on XR saw a markedly greater reduction in GI symptoms. The XR group's superior tolerability is clinically important, as GI side effects are a leading cause of metformin discontinuation (approximately 5% of patients cannot tolerate metformin at all).[8,17] Our real-world data suggest that using the XR formulation can mitigate this issue and help patients remain on therapy.

These results are consistent with several prior studies. For example, a 2021 meta-analysis of randomized trials and real-world studies reported that XR was associated with improved compliance and (in several comparisons) fewer GI events than IR.[9,14] Similarly, a 2024 systematic review and meta-analysis of observational studies found that XR metformin is associated with significantly lower rates of GI adverse events compared to IR, including bloating, abdominal pain, constipation, diarrhea, and vomiting.[8] Another randomized trial demonstrated that metformin XR, even at the highest doses, resulted in fewer gastrointestinal complaints and was better tolerated than IR.[18]

On the other hand, not all comparisons have shown a large divergence: the CONSENT trial in China (a large 16-week RCT) found that GI adverse event rates were roughly equivalent between XR and IR (23.8% vs 22.3%, respectively),[19] while achieving noninferior glycemic efficacy.[9] The authors of that study noted that careful dose titration and cultural dietary factors might have attenuated differences in GI outcomes. Additionally, another 2021 review found a reduction in GI adverse events with metformin IR compared to XR; however, this finding was not statistically significant in their systematic review and meta-analysis.[17]

Despite such findings, XR is generally regarded as less taxing on the GI tract, especially in long-term use. Our study's observation that XR patients had fewer incidents of diarrhea, constipation, and overall symptom burden reinforces this general trend. The importance of GI tolerability has spurred the development of novel formulations, such as delayed-release metformin (Met DR), which target drug delivery to the lower bowel to minimize upper GI exposure.[11,17] Taken together, the evidence (including our results) indicates that XR metformin provides a tangible reduction in GI side effects for many patients, which can enhance patient comfort and persistence with therapy.

Treatment satisfaction: Crucially, improved tolerability with XR translated into better patient-reported outcomes in our cohort. Patients on XR reported significantly higher TS after 6 months compared to those on IR, as measured by the OHA-Q ver. 2 questionnaire. In particular, the XR group had a median TS score of 100 (indicating very high satisfaction) vs 78 in the IR group, and they reported fewer bothersome side effects on the SS subscale. This aligns with the intuitive expectation that a formulation causing fewer side effects and requiring one or 2 daily doses would be more satisfying to patients.[9,17] Our study provides empirical support for that assumption. To our knowledge, few studies prior to ours have explicitly compared patient satisfaction between IR and XR metformin. The improvement we observed is notable because satisfaction with medication is a key determinant of adherence and long-term therapy success. In qualitative terms, many XR patients in our study were essentially "very satisfied" with their treatment, whereas IR patients, while improved over baseline, were more often only "somewhat satisfied." This difference is clinically meaningful, as higher satisfaction tends to foster better compliance and persistence.[9,14]

In this study, we did not focus on medication adherence, as it could be directly measured by pill counts for all patients. However, the combination of fewer side effects, simpler dosing, and higher satisfaction with XR strongly suggests better adherence over time. Extensive diabetes research has shown that regimen complexity and side-effect burdens are major barriers to adherence.[9,20] Real-world and population-based data

indicate that simple daily dosing or improved tolerability can significantly improve adherence and persistence compared to more complex regimens.[9,14,21] For instance, meta-analysis and review evidence show higher compliance with XR versus IR metformin.[9,14] Likewise, contemporary cohorts have demonstrated a link between better adherence and improved clinical status and patient-reported outcomes.[22,23] Tan et al (2021) conducted a systematic review and meta-analysis, finding that metformin XR improved patients' satisfaction and adherence to their treatment.[9] Derosa et al (2017) found, in their randomized controlled trial, that patients on metformin XR experienced better TS than their counterparts on metformin IR.[18]

Although our study was not designed to rigorously quantify adherence, these external findings support the inference that the XR group's experience would likely promote better long-term adherence. Improved adherence, in turn, has well-documented benefits: patients who consistently take their medications have better glycemic control and a lower risk of complications and adverse outcomes.[22,23] Therefore, the advantages of XR in tolerability and convenience, as seen in our study, are not merely a matter of comfort. They can reasonably be expected to yield better clinical outcomes in the long run, simply because patients "take it more reliably and are happier with their therapy." (as we hypothesized at the outset).

Quality of life: Interestingly, despite the clear differences in side-effect profiles and TS, overall diabetes-related quality of life (QoL) improvements were similar in the XR and IR groups. Both groups showed significant increases in their DTR-QOL global scores over 6 months, and the between-group difference in QoL was not statistically significant. There are several possible explanations for this. First, QoL is a multifaceted construct; while GI discomfort and pill burden affect QoL, other factors, such as achieving glycemic control, receiving education, and adjusting to living with diabetes, play a significant role in the first few months after diagnosis. It appears that both the XR and IR patients, as newly diagnosed diabetics, experienced improved QoL as their blood glucose was controlled and they became more confident in managing their condition. Second, the DTR-QOL instrument focuses on broad domains (physical functioning, psychological burden, TS, etc), and it may not be highly sensitive to the subtle differences in daily comfort between XR and IR, especially once acute side effects wane in both groups. It is notable that in our results, the specific domain related to treatment discomfort (the OHA-Q "SS" subscale) showed a significant difference in favor of XR, reflecting the lower side-effect burden. However, improvements in other domains (e.g., "burden on daily activities") were observed in both groups and tended to offset the total QoL score. Third, the duration of 6 months might be too short to detect divergent trajectories in QoL. Many participants had relatively high QoL scores by study end (median ~85–88/100), leaving little room for a detectable difference ("ceiling effect"). It is plausible that, over a more extended period, patients on XR might maintain a higher QoL if those on IR begin to experience frustration with ongoing side effects or regimen complexity. Additionally, any long-term benefits of better adherence (e.g., fewer diabetes complications or hospitalizations) would ultimately contribute to QoL; however, such outcomes would not be expected within a 6-month window.

Notably, recent cross-sectional and cohort data demonstrate significant associations between better adherence and improved QoL among people with T2DM, supporting the view that formulation-driven adherence gains could translate into QoL benefits over time.[21–23] Al Hayek et al (2014) noted that, among Saudi patients with T2DM, factors like treatment complexity and side effect frequency were associated with lower health-related QoL.[24] This suggests that a regimen that is simpler and gentler (as XR metformin) should, in theory, improve QoL primarily by reducing treatment-related stress and discomfort. We did not see a large QoL gap in our study because, as discussed, both groups ultimately received relatively simplified treatment (metformin-only therapy) and experienced benefits from improved diabetes control. Moreover, many participants were early in their disease course with few comorbidities, which is when QoL tends to be high overall. It is also worth noting that quality of life and adherence have a reciprocal relationship. Patients who tolerate their medications and find them convenient are more adherent, and those who adhere better often report higher QoL. In summary, while both IR and XR metformin improved patients' diabetes-related QoL substantially (likely due to effective disease management), the XR's key benefits were captured in metrics of TS and tolerability rather than in the broad QoL measure. These patient-centered benefits remain critically important, as they can significantly influence long-term engagement with therapy.

From a clinical perspective, the advantages of metformin XR observed in this study have meaningful implications. Foremost, using XR can help patients stay on metformin, which is the cornerstone of T2DM management, thereby avoiding premature therapeutic escalation. Therapeutic inertia and poor glycemic control remain a major problem in diabetes care, often because patients are unable or unwilling to continue first-line treatments due to side effects or inconvenience. Our findings, together with contemporary reviews, suggest that starting with an XR formulation (or switching to XR early in the course) can alleviate 2 key barriers to effective therapy (side effects and dosing frequency), which in turn promote better adherence and persistence.[9,17] Over the long term, this could translate into improved glycemic outcomes and a lower risk of complications. There may be a slightly higher cost for XR formulations, but this may be offset by downstream benefits. While country-specific analyses for Saudi Arabia are dated, recent narrative and practical reviews reaffirm metformin's overall cost-effectiveness and support optimization strategies (including use of XR when intolerance to IR is an issue).[25,26] By enhancing tolerability without compromising efficacy, metformin XR can improve the patient experience and likely the long-term success of T2DM treatment. This patient-centered benefit is aligns with the broader goals of diabetes care, which emphasize not only glycemic targets but also quality of life and TS.[25,27]

5. Conclusion

In conclusion, XR metformin demonstrated superior GI tolerability and greater patient satisfaction compared to IR metformin in this cohort of patients with T2DM. While both formulations were effective in improving diabetes-specific quality of life and presumably glycemic control over 6 months, the XR formulation's reduced side effect burden and simpler dosing schedule provided a clear benefit in terms of TS and convenience. These findings underscore the clinical value of metformin XR as a first-line or alternative therapy for patients who have difficulty with IR metformin. By minimizing uncomfortable side effects and enhancing adherence, XR metformin can improve the overall patient experience and potentially lead to better long-term clinical outcomes. Clinicians should consider these patient-centered benefits when selecting a metformin formulation, especially for individuals who are prone to GI side effects or have struggled with medication adherence. Ultimately, optimizing tolerability and satisfaction with therapy is an important component of managing chronic diseases like diabetes, and our results support the preferential use of metformin XR to achieve these goals without compromising efficacy.

5.1. Study limitations

This study has several limitations that should be considered when interpreting the findings. As an observational cohort rather than a randomized controlled trial, treatment allocation to IR or XR metformin was based on real-world prescribing, introducing potential selection bias and unmeasured confounding. The

modest sample size (119 patients) was adequate for detecting significant differences in GI tolerability and satisfaction but may have lacked power for smaller effects, such as subtle QoL differences. The 6-month follow-up period may have been too short to capture long-term outcomes, such as sustained satisfaction, adherence, or reduction in complications. Adherence was not objectively measured for all patients, limiting direct confirmation of its improvement with XR. The single-center Saudi setting with all participants being nationals may limit the generalizability of the findings to other populations with different demographics, health systems, or cultural factors. Additionally, a 16% attrition rate could have introduced bias if dropouts were related to study outcomes, despite no marked imbalance between groups. Overall, these factors warrant cautious interpretation, and future randomized, longer-term, and multi-center studies with objective adherence measures would help strengthen the evidence on XR's advantages over IR metformin.

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