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Longitudinal Changes in Insulin Resistance Indices During SGLT2 Inhibitor Therapy in Type 2 Diabetes: A Prospective Observational Cohort Study

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Abstract

Background/Objectives: Glucose-lowering treatment can change insulin resistance indices without demonstrating improved insulin sensitivity. We described these changes during sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy in routine care. **Methods:** In this prospective, uncontrolled observational cohort, 54 adults with type 2 diabetes were assessed at baseline, 3 and 6 months. Background medication was abstracted from hospital and prescription records. Exploratory baseline-to-6-month comparisons used Wilcoxon signed-rank tests with Benjamini–Hochberg adjustment across 15 analysed outcomes. **Results:** Median HOMA-IR decreased from 8.38 (IQR 3.47–13.26) to 3.14 (2.19–4.39), a 62.6% reduction in group medians (rank-biserial r = −0.79; adjusted $p < 0.001$); in the 41 participants without documented insulin use, the reduction was 50.9% (r = −0.76). Median triglyceride–glucose (TyG) index decreased from 9.45 to 9.04 (−4.3%; r = −0.63; adjusted $p < 0.001$). Change in HOMA-IR was not significantly correlated with change in HbA1c ($\rho = -0.15$; $p = 0.27$). **Conclusions:** Both indices decreased during follow-up, including in participants without documented insulin use, but these observations cannot establish a treatment effect or improved insulin sensitivity. TyG requires no insulin measurement but remains sensitive to glucose- and triglyceride-lowering therapies, including SGLT2 inhibitors. Controlled studies with direct measures of insulin sensitivity are needed.

Keywords: SGLT2 inhibitor; insulin resistance; HOMA-IR; triglyceride–glucose index; C-peptide; type 2 diabetes; reduced kidney function

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1. Introduction

Insulin resistance is a fundamental pathophysiological abnormality underlying the development and progression of type 2 diabetes mellitus (T2DM) and contributes substantially to cardiovascular disease, chronic kidney disease (CKD), and premature mortality [1–3]. Although glycaemic control remains a principal therapeutic target, residual cardiometabolic risk frequently persists despite improvements in glycated haemoglobin (HbA1c), suggesting that mechanisms beyond glucose lowering influence long-term clinical outcomes [4]. Consequently, improving insulin resistance has emerged as an important therapeutic objective alongside conventional glycaemic management.

Accurate assessment of insulin resistance is therefore essential for evaluating metabolic risk and treatment response in patients with T2DM. The Homeostatic Model Assessment of

Insulin Resistance (HOMA-IR) is a well-established surrogate marker of hepatic insulin resistance but requires fasting insulin measurements, limiting its routine clinical applicability [2,5]. In contrast, the triglyceride–glucose (TyG) index is derived from routinely available laboratory parameters and has emerged as a simple, reproducible surrogate marker associated with insulin resistance, metabolic syndrome, and adverse cardiovascular outcomes [6–12]. Some insulin resistance surrogates have also been associated with long-term all-cause or cardiovascular mortality in large population-based cohorts [13,14]. Because these indices reflect complementary aspects of metabolic dysfunction, their combined longitudinal assessment may provide a more comprehensive evaluation of treatment response than either marker alone.

Large randomised clinical trials have established that sodium–glucose cotransporter-2 (SGLT2) inhibitors reduce cardiovascular events, slow CKD progression, and improve survival in patients with T2DM [15–24]. These benefits are reflected in current consensus recommendations positioning SGLT2 inhibitors as foundational therapy in type 2 diabetes [25], with meta-analytic evidence confirming consistent cardiovascular protection across the cardiometabolic disease spectrum [26], alongside evidence of reduced kidney-failure risk [27]. Beyond glucose lowering, these agents have been reported to improve insulin sensitivity and albuminuria, and haematological and other cardiometabolic changes have been proposed to contribute to their cardiovascular benefit [28–32]. Nevertheless, prospective real-world data evaluating longitudinal changes in validated surrogate markers of insulin resistance remain limited, particularly regarding the complementary behaviour of HOMA-IR and the TyG index and the potential influence of kidney function on these metabolic responses. Recent experimental work in human cardiac tissue identified direct activation of pantothenate kinase 1 (PANK1), a rate-limiting enzyme in coenzyme A synthesis, as a potential mechanism linking SGLT2 inhibition with altered fuel metabolism [33]. Its relevance to systemic insulin resistance in routine diabetes care remains to be established.

We conducted a prospective six-month observational cohort study in adults with T2DM initiating SGLT2 inhibitor therapy in routine care to describe changes in HOMA-IR, the triglyceride–glucose (TyG) index and other metabolic and laboratory measures. The present analyses are exploratory. HOMA-IR requires a fasting insulin measurement and is affected by exogenous insulin therapy. TyG requires no insulin measurement, but insulin therapy can influence both of its components and SGLT2 inhibitors directly lower glucose. We therefore evaluate these indices as longitudinal biochemical measures rather than as independent confirmation of improved insulin sensitivity. The uncontrolled design does not permit attribution of changes to SGLT2 inhibition.

2. Materials and Methods

2.1. Study Design and Population

This prospective, single-centre, real-world cohort study was conducted at Osmaniye Training and Research Hospital, Osmaniye, Türkiye. Consecutive adults (≥18 years) with established type 2 diabetes mellitus (T2DM) who initiated sodium–glucose cotransporter-2 inhibitor (SGLT2i) therapy in January 2026 were prospectively included and followed for six months. Final six-month follow-up assessments were completed in July 2026. Consecutive inclusion was used to minimise selection bias and enhance the external validity of the findings by reflecting routine clinical practice. The study was observational and non-interventional. No treatment was allocated, assigned, randomised or modified for research purposes: the decision to start an SGLT2 inhibitor, and the choice of agent and dose, were made by the treating physician as part of routine diabetes care, before and independently of inclusion in this study, and the three assessments and their laboratory measurements were part of the clinic's routine monitoring practice; the study introduced no additional

procedure, visit or exposure beyond routine care. Because no intervention was prospectively assigned, the study does not meet the ICMJE definition of a clinical trial and was accordingly not registered in a trial registry. The report follows the STROBE recommendations for observational cohort studies.

Eligible participants had a confirmed diagnosis of T2DM and initiated SGLT2 inhibitor therapy according to the clinical judgement of their treating physician and current international guideline recommendations. Exclusion criteria included type 1 diabetes mellitus, pregnancy, active acute illness, previous SGLT2 inhibitor use within the preceding three months, and missing HOMA-IR or TyG data required for the present exploratory analyses.

Of 61 consecutive patients assessed for eligibility, 56 were enrolled; the individual reasons for non-enrolment of the remaining 5 were not captured in the study dataset and are therefore not reported, which is acknowledged as a limitation of the screening records. Of the 56 enrolled participants, one was lost to follow-up, and one declined the repeat examination; the remaining 54 underwent all three scheduled assessments and constitute the analytical cohort. Participant flow, including per-variable data availability, is shown in Figure 1. The agent prescribed by the treating physician was dapagliflozin 10 mg in 45 participants (83.3%) and empagliflozin 25 mg in 9 (16.7%) (Table 1); neither the agent nor the dose was assigned by the investigators. All 54 participants in the analytical cohort completed the baseline, month-3 and month-6 assessments. Analyses were complete-case, without imputation.

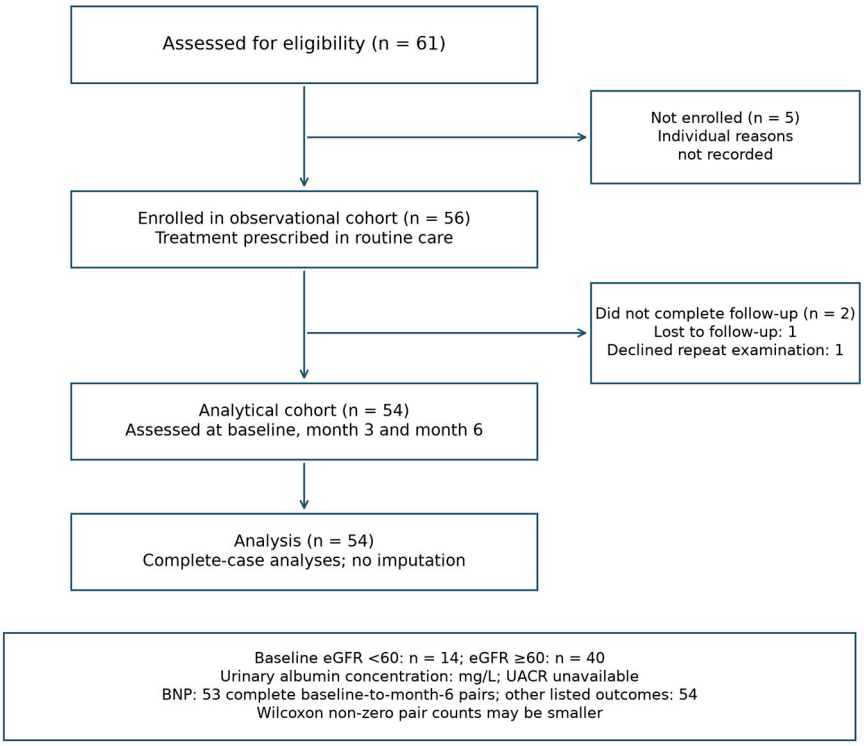


Figure 1. Participant flow. Of 61 screened patients, 56 were enrolled; reasons for non-enrolment of five patients were not recorded. One enrolled participant was lost to follow-up, and one declined the repeat examination, leaving 54 participants who were assessed at baseline, month 3 and month 6 and analysed. Kidney subgroups use baseline eGFR alone. The urine variable is albumin concentration in mg/L, not UACR. BNP has 53 complete baseline-to-month-6 pairs; the other 14 outcomes in Table 2 have 54. Wilcoxon tests exclude zero differences.

Table 1. Baseline characteristics ($n = 54$).

Variable	Value
Age (years), mean ± SD	61.8 ± 9.2
Female sex, *n* (%)	31 (57.4)
eGFR <60 mL/min/1.73 m^2, *n* (%)	14 (25.9)
eGFR ≥60 mL/min/1.73 m^2, *n* (%)	40 (74.1)
Dapagliflozin 10 mg, *n* (%)	45 (83.3)
Empagliflozin 25 mg, *n* (%)	9 (16.7)
Diabetes duration (years), median (IQR)	2.5 (1.0–6.0)
Hypertension, *n* (%)	30 (55.6)
Coronary artery disease, *n* (%)	2 (3.7)
Heart failure, stroke or peripheral artery disease, *n* (%)	0 (0)
Insulin, *n* (%)	13 (24.1)
Metformin, *n* (%)	45 (83.3)
DPP-4 inhibitor, *n* (%)	25 (46.3)
Pioglitazone, *n* (%)	12 (22.2)
Sulfonylurea, *n* (%)	5 (9.3)
GLP-1 receptor agonist, *n* (%)	0 (0)
Statin, *n* (%)	46 (85.2)
ACE inhibitor or ARB, *n* (%)	26 (48.1)
Diuretic, *n* (%)	9 (16.7)
HOMA-IR, median (IQR)	8.38 (3.47–13.26)
TyG index, median (IQR)	9.45 (9.16–9.99)
HbA1c (%), median (IQR)	7.35 (6.73–9.25)
Fasting glucose (mg/dL), median (IQR)	147 (116–194)
Fasting insulin (μU/mL), median (IQR)	22.0 (10.0–32.0)
Uric acid (mg/dL), median (IQR)	5.70 (4.55–6.88)
GGT (U/L), median (IQR)	20.0 (15.0–28.8)
Haemoglobin (g/dL), median (IQR)	13.05 (12.03–14.28)
eGFR (mL/min/1.73 m^2), median (IQR)	89.00 (59.75–97.00)
eGFR (mL/min/1.73 m^2), mean ± SD	80.0 ± 22.7
Urinary albumin (mg/L), median (IQR)	12.50 (5.53–52.73)
Total cholesterol (mg/dL), median (IQR)	196.00 (173.25–221.25)
HDL-C (mg/dL), median (IQR)	50.50 (44.00–57.00)
LDL-C (mg/dL), median (IQR)	109.50 (89.25–128.75)
Albumin (g/L), median (IQR)	42.00 (40.00–44.00)
Creatinine (mg/dL), median (IQR)	0.80 (0.70–1.03)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TyG, triglyceride–glucose. Medication and comorbidity data were abstracted from hospital and national prescription records; diabetes duration and the SGLT2 inhibitor were taken from the baseline data-collection form (Supplementary Data S1c). Body weight, body mass index, blood pressure and smoking status were not recorded in the source records. LDL-C is reported as provided by the laboratory; the analytical or calculation method was not available.

Table 2. Longitudinal changes in metabolic parameters ($n = 54$).

Parameter	Baseline, Median (IQR)	Month 3, Median (IQR)	Month 6, Median (IQR)	*n* Non-Zero Pairs	r	*p*	BH *p*	Change, %
HOMA-IR	8.38 (3.47–13.26)	3.37 (2.27–6.17)	3.14 (2.19–4.39)	54	−0.79	<0.001	<0.001	−62.6
Fasting insulin (μU/mL)	22.00 (10.00–32.00)	10.10 (7.20–17.00)	11.00 (7.25–13.00)	52	−0.71	<0.001	<0.001	−50.0
C-peptide (ng/mL)	2.92 (1.72–5.05)	2.30 (1.50–2.80)	1.95 (1.53–2.98)	51	−0.61	<0.001	<0.001	−33.2
Fasting glucose (mg/dL)	147.00 (116.25–194.25)	123.50 (107.25–149.25)	116.50 (101.25–134.75)	53	−0.63	<0.001	<0.001	−20.7
TyG index	9.45 (9.16–9.99)	9.10 (8.77–9.48)	9.04 (8.76–9.38)	54	−0.63	<0.001	<0.001	−4.3

Table 2. *Cont.*

Parameter	Baseline, Median (IQR)	Month 3, Median (IQR)	Month 6, Median (IQR)	*n* Non-Zero Pairs	r	*p*	BH *p*	Change, %
HbA1c (%)	7.35 (6.73–9.25)	7.15 (6.63–8.18)	7.20 (6.63–8.30)	51	−0.51	0.002	0.003	−2.0
Triglycerides (mg/dL)	168.00 (120.25–239.75)	140.00 (99.75–196.25)	158.50 (106.25–189.00)	53	−0.46	0.004	0.006	−5.7
Uric acid (mg/dL)	5.70 (4.55–6.88)	5.00 (3.70–5.78)	4.90 (4.00–6.08)	54	−0.53	<0.001	0.001	−14.0
GGT (U/L)	20.00 (15.00–28.83)	19.50 (15.00–26.00)	16.50 (13.00–23.75)	52	−0.41	0.010	0.016	−17.5
ALT (U/L)	20.00 (13.25–24.75)	18.00 (14.00–23.00)	18.50 (13.00–24.00)	51	−0.27	0.088	0.119	−7.5
FIB−4 index	1.10 (0.80–1.32)	1.05 (0.86–1.34)	0.99 (0.83–1.34)	54	−0.07	0.664	0.711	−10.0
eGFR (mL/min/1.73 m^2)	89.00 (59.75–97.00)	91.50 (66.50–98.00)	91.50 (63.75–98.00)	51	+0.26	0.111	0.138	+2.8
Urinary albumin (mg/L)	12.50 (5.53–52.73)	12.50 (6.00–35.00)	12.00 (5.40–53.00)	54	+0.04	0.806	0.806	−4.0
BNP (pg/mL)	47.00 (23.00–78.00)	39.50 (19.25–62.00)	36.00 (17.25–55.75)	53	−0.23	0.143	0.165	−23.4
Haemoglobin (g/dL)	13.05 (12.03–14.28)	13.35 (12.53–14.38)	13.70 (12.70–14.68)	49	+0.69	<0.001	<0.001	+5.0

Values are median (IQR). *n* is the number of non-zero paired differences used in the Wilcoxon test; the measured pair count is 54 except BNP (53). r is the paired rank-biserial correlation. BH-adjusted *p* values refer only to the 15 baseline-to-6-month comparisons listed here; the expanded 17-test sensitivity analysis is in Table S5. Change (%) is the percentage difference between group medians, not the median of individual changes. HbA1c is expressed as a percentage; its percentage change is relative, not a change in percentage points. Abbreviations: ALT, alanine aminotransferase; BH, Benjamini–Hochberg; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 index; GGT, gamma-glutamyl transferase; HbA1c, glycated haemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IQR, interquartile range; TyG, triglyceride–glucose.

2.2. Baseline Kidney Function and Subgroup Classification

Exploratory kidney-function subgroups were defined solely by baseline eGFR <60 versus ≥60 mL/min/1.73 m^2, using the eGFR threshold described in KDIGO guidance [34]. The urine measurement was albumin concentration (mg/L), not urinary albumin-to-creatinine ratio (UACR). No urinary creatinine measurement was available, so UACR and its ≥30 mg/g threshold could not be calculated or applied. The previous UACR-based classification was therefore withdrawn. The clinician-coded baseline CKD field (13 participants) was retained in the source data for provenance but was not treated as equivalent to the calculated reduced-eGFR group. The separate HERMES article (Section 2.6) classifies the same participants by a prespecified chronic low-eGFR criterion (CKD-positive, $n = 13$; CKD-negative, $n = 41$). The two classifications differ by one participant, who had a single baseline eGFR <60 without documented chronicity and is in the eGFR <60 group here and in the CKD-negative group in HERMES. A single eGFR assessment does not establish chronic kidney disease. All subgroup analyses were defined during revision and are exploratory.

2.3. Variables and Derived Indices

Venous blood samples were obtained after an overnight fast of at least 8 h at each assessment. Biochemistry tests were performed on an AU5800 Chemistry Analyzer (Beckman Coulter Inc., Brea, CA, USA), hormone tests on a UniCel DxI 800 Access Immunoassay System (Beckman Coulter Inc., Brea, CA, USA) and HbA1c on an HLC-723G11 Automated Glycohemoglobin Analyzer (Tosoh Corporation, Tokyo, Japan). The primary analysis dataset (Supplementary Data S1) contains fasting insulin (μU/mL), C-peptide (ng/mL), fasting plasma glucose (mg/dL), HbA1c (%), triglycerides (mg/dL), uric acid (mg/dL), AST, ALT and GGT (U/L), eGFR (mL/min/1.73 m^2), urinary albumin concentration (mg/L), B-type natriuretic peptide (BNP; pg/mL), haemoglobin (g/dL) and platelet count (10^9/L), together with the derived indices described below. Total cholesterol (mg/dL), HDL-C

(mg/dL), LDL-C (mg/dL), serum albumin (g/L) and creatinine (mg/dL) were measured in the same routine samples but were not part of the original analysis dataset; during revision they were retrieved from the source laboratory workbook, linked to Supplementary Data S1 by participant, and are provided as Supplementary Data S1b. LDL-C is reported as provided by the laboratory; the analytical or calculation method was not available. The original manuscript listed these five analytes without reporting results; this has been corrected. The source formula used to report eGFR was not included in Supplementary Data S1.

Background medication and comorbidities were not part of the original analysis dataset. During revision, they were abstracted for all 54 participants from the hospital information system and the national electronic prescription system (0–6-month prescription history) and compared with the medication list recorded in the study source sheet at inclusion. Diabetes duration and the prescribed SGLT2 inhibitor were taken from the study's baseline data-collection form. Nine discordant entries in eight participants (insulin in two, metformin in three, pioglitazone in one and hypertension in three) were resolved by review of the original records. Insulin use was classified from the records at baseline and at month 6; insulin doses, dose changes and the timing of any change between these visits were not recorded, so interim insulin exposure was not verified. Changes in other glucose-lowering agents (start, stop or dose change) were taken from the record form; for the three participants whose form entry for an agent was overturned by record review, the corresponding change field was treated as unknown rather than as no change. Dispensed quantities, body weight, height, blood pressure and smoking status were not recorded in a form that could be abstracted. These data are provided as Supplementary Data S1c.

Derived indices were calculated as follows: HOMA-IR = fasting plasma glucose [mg/dL] × fasting insulin [μU/mL]/405; TyG = ln(fasting triglycerides [mg/dL] × fasting plasma glucose [mg/dL]/2); and FIB-4 = age × AST/(platelet count × √ALT). HOMA-IR and TyG were evaluated as surrogate biochemical indices; TyG is insulin-measurement-independent. These measures were interpreted with the limitations that exogenous insulin can compromise HOMA-IR and changes in either TyG component can change the index without establishing a change in insulin sensitivity. FIB-4 was analysed as a non-invasive liver-related index; its AST and platelet components were also considered in an expanded multiplicity sensitivity analysis.

2.4. Statistical Analysis

Analyses were regenerated in Python 3.11.15 using NumPy 2.4.6, SciPy 1.17.1 and statsmodels 0.14.6, with pandas (https://pandas.pydata.org, accessed on 1 November 2026) for data handling and Matplotlib (https://matplotlib.org, accessed on 1 November 2026) for figures; the recorded software versions and a reproducible revision script are supplied. Continuous variables are summarised as median (IQR), or mean ± SD for age. Baseline-to-6-month changes were tested with two-sided Wilcoxon signed-rank tests, excluding zero differences. The non-zero pair count can therefore be smaller than the measured pair count. Paired rank-biserial correlations are $(W+ - W-)/(W+ + W-)$, with 95% percentile bootstrap confidence intervals from 4000 participant resamples. Percentage changes describe the difference between group medians divided by the baseline median; they are not medians of individual percentage changes. The original analysis-stage family of 15 outcome comparisons, listed explicitly in Table 2, was retained for Benjamini–Hochberg (BH) adjustment. This was not a prospectively registered family and does not comprise every measured analyte. AST and platelet count were available as FIB-4 components; an expanded 17-comparison sensitivity family is provided in Table S5. The five additional laboratory series were analysed as a separate five-test BH family and in a 22-test sensitivity family combining them with the 17 comparisons of Table S5 (Tables S8 and S9). No choice of

family was made on the basis of statistical significance. All six pairwise visit comparisons for HOMA-IR and TyG shown in Figure 2 form a separate exploratory BH family (Table S6). The baseline-to-6-month adjusted p value in this six-test family differs from that in Table 2 because the families answer different sets of questions. Longitudinal mixed models used categorical time and participant-specific random intercepts, with log-transformed HOMA-IR and untransformed TyG. Pooled time effects are reported for the full cohort; separate kidney-criterion-by-time models are exploratory and appear in Table S4. Between-group change comparisons used Mann–Whitney U tests, and change-score association used Spearman correlation. Medication-based sensitivity analyses followed a written analysis plan prepared during revision, which is not a preregistration: baseline-to-6-month comparisons were repeated in participants without documented insulin use at baseline or month 6 and in those who also had a documented absence of change in other glucose-lowering therapy (unknown change fields excluded), and participants with documented insulin use were described separately. The plan classified participants with conflicting sources as having unknown insulin exposure; because these entries were subsequently resolved by record review, the analysis restricted to participants without insulin in either source before record review is also reported. Model, subgroup, correlation, medication-based and insulin-threshold sensitivity p values are nominal and not multiplicity adjusted. Two-sided $p < 0.05$ was used as a descriptive threshold, without confirmatory inference. Complete-case analyses used the data available for each comparison, without imputation. The revised script regenerates Tables 1–3, Figures 1–5 and the Supplementary Analyses.

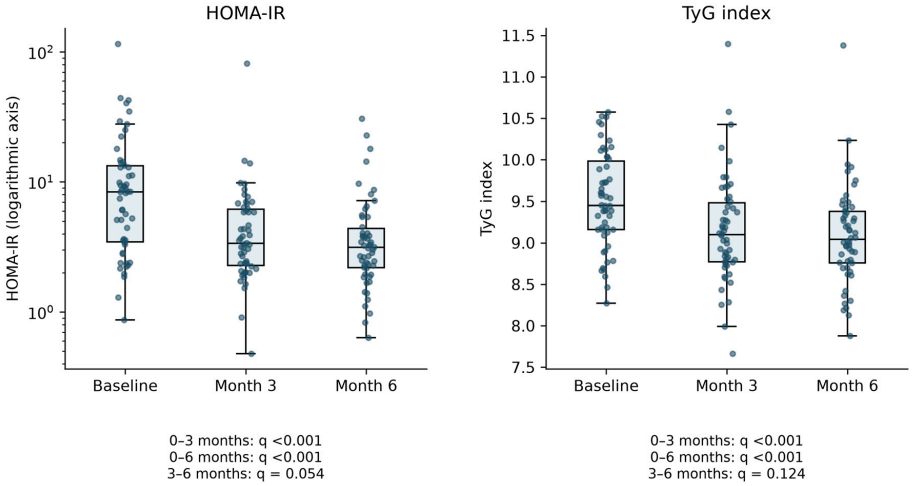


Figure 2. Distributions of HOMA-IR and TyG at baseline, month 3 and month 6 ($n = 54$). Boxes show median and IQR; whiskers extend to 1.5 × IQR. Every measured value is shown as a jittered point. The HOMA-IR axis is logarithmic to retain all observations without compressing most values. The displayed q values derive from two-sided Wilcoxon signed-rank tests followed by BH adjustment across all six visit-pair comparisons for both indices together. This exploratory family is distinct from the 15-outcome family in Table 2. All comparisons, including non-significant ones, are retained. Full results are in Table S6.

Table 3. Sensitivity analyses based on medication records and on arbitrary fasting-insulin exclusion thresholds.

Scenario	*n*	Outcome	Baseline Median	Month 6 Median	Change, %	r	*p*
All participants	54	HOMA-IR	8.38	3.14	−62.6	−0.79	<0.001
All participants	54	TyG index	9.45	9.04	−4.3	−0.63	<0.001
No insulin documented at baseline or month 6	41	HOMA-IR	6.15	3.02	−50.9	−0.76	<0.001

Table 3. *Cont.*

Scenario	*n*	Outcome	Baseline Median	Month 6 Median	Change, %	r	*p*
No insulin documented at baseline or month 6	41	TyG index	9.46	9.00	−4.8	−0.77	<0.001
As above, and documented no change in other glucose-lowering therapy	39	HOMA-IR	7.47	3.12	−58.3	−0.77	<0.001
As above, and documented no change in other glucose-lowering therapy	39	TyG index	9.54	9.00	−5.6	−0.79	<0.001
No insulin in either source before record review	40	HOMA-IR	6.81	3.07	−54.9	−0.76	<0.001
No insulin in either source before record review	40	TyG index	9.50	9.01	−5.2	−0.76	<0.001
Insulin use documented (descriptive)	13	HOMA-IR	9.60	3.47	−63.8	−0.85	0.005
Insulin use documented (descriptive)	13	TyG index	9.33	9.42	+1.0	−0.19	0.588
Exclude fasting insulin above 100 µU/mL at any visit	50	HOMA-IR	7.84	3.07	−60.9	−0.75	<0.001
Exclude fasting insulin above 100 µU/mL at any visit	50	TyG index	9.45	9.01	−4.6	−0.70	<0.001
Exclude fasting insulin above 50 µU/mL at any visit	46	HOMA-IR	6.13	3.07	−50.0	−0.71	<0.001
Exclude fasting insulin above 50 µU/mL at any visit	46	TyG index	9.39	9.01	−4.0	−0.65	<0.001

p values are nominal two-sided Wilcoxon signed-rank values for every row, without BH adjustment; the full-cohort BH-adjusted results are given separately in Table 2. Percentage changes are differences between group medians relative to the baseline median. Insulin status is based on hospital and national prescription records at baseline and month 6, with discordant entries resolved by record review; interim exposure was not verified. Change fields that could not be established were treated as unknown and excluded from the no-change row. HOMA-IR in participants with documented insulin use is descriptive only. Fasting-insulin thresholds cannot establish the presence or absence of exogenous insulin use. Abbreviations: BH, Benjamini–Hochberg; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TyG, triglyceride–glucose.

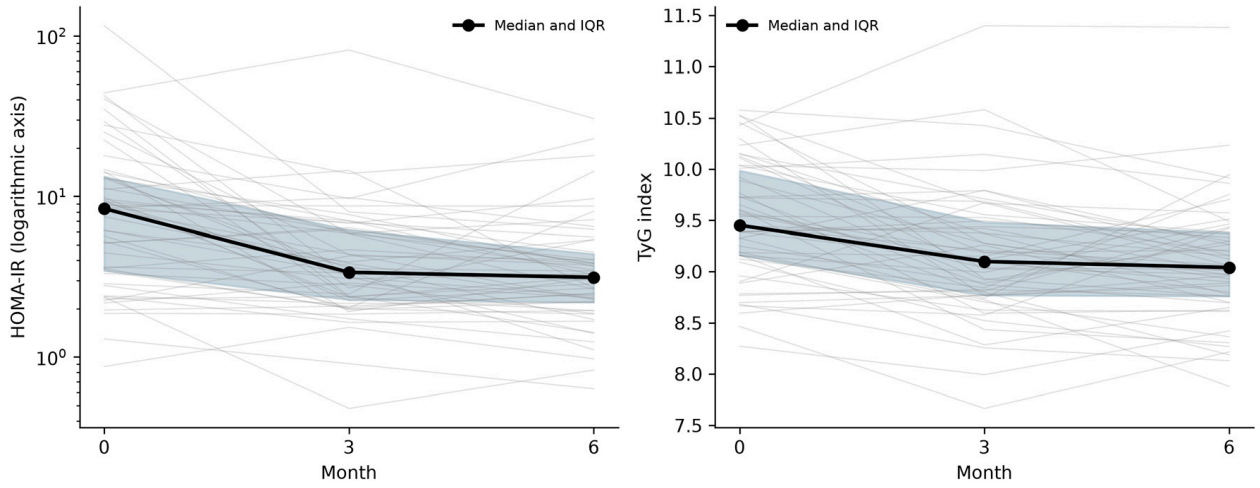


Figure 3. Individual trajectories of HOMA-IR and TyG across the three assessments (n = 54). Grey lines show individual participants; the black line shows the group median and the shaded band the IQR. The HOMA-IR axis is logarithmic. These descriptive trajectories do not establish treatment effects.

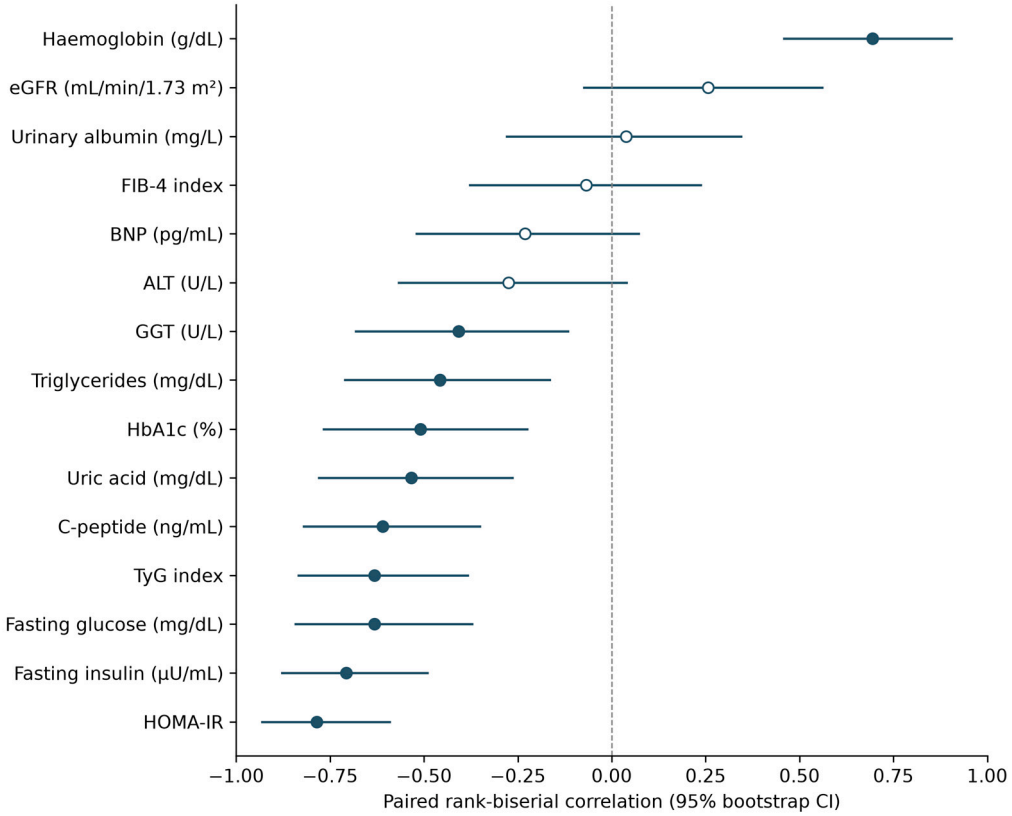


Figure 4. Paired rank-biserial effect sizes for baseline-to-6-month changes in the 15 analysed outcomes. Bars show 95% percentile bootstrap confidence intervals from 4000 participant resamples. Filled markers indicate BH-adjusted $p < 0.05$ in the 15-outcome family; open markers indicate $p \geq 0.05$. Negative values indicate decreases. HOMA-IR is affected by exogenous insulin in the 13 participants with documented insulin use, and TyG is sensitive to changes in its glucose and triglyceride components.

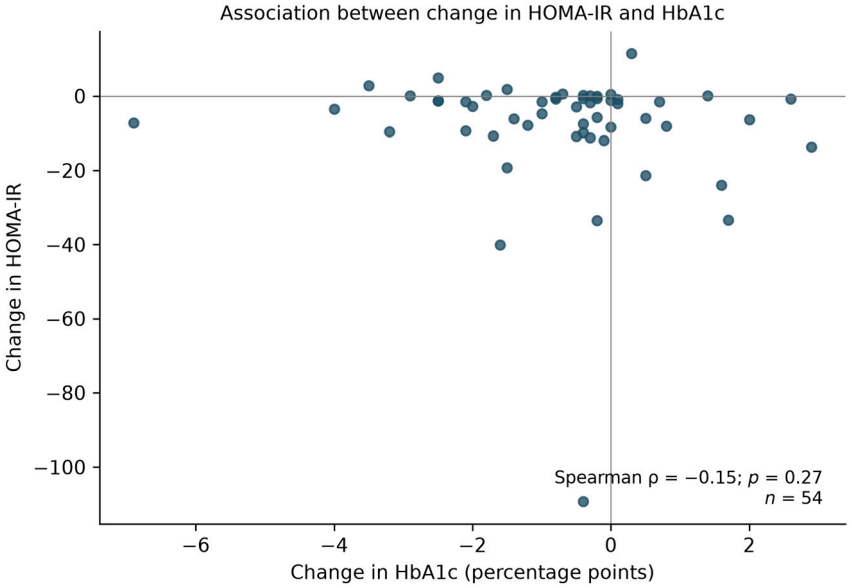


Figure 5. Association between change in HOMA-IR and change in HbA1c from baseline to month 6. Each point represents a participant ($n = 54$). Spearman $\rho = -0.15$; nominal $p = 0.27$. HbA1c change is expressed in percentage points. The non-significant association does not demonstrate independence. No fitted regression line or confidence band is shown.

2.5. Sample Size and Power Analysis

HOMA-IR and TyG were not the primary outcome of the approved study protocol, and no endpoint-specific sample-size justification was made for them; these analyses are therefore presented as exploratory. The protocol designated hepatic steatosis as its primary outcome, and its sample-size calculation related to that outcome, which is reported separately. We do not infer adequate power from the observed changes. To illustrate planning for a future paired study, a hypothetical HOMA-IR decrease of 2 units would require 34, 73 or 199 complete pairs if the SD of the paired change were 4, 6 or 10 units, respectively (two-sided $\alpha = 0.05$, 80% power, paired t-test approximation; Table S7). These scenarios were calculated during revision, were not used to determine recruitment, and do not constitute an a priori or Wilcoxon-specific power calculation.

2.6. Ethics

The study was approved by the Health Sciences Research Ethics Committee of Osmaniye Korkut Ata University (approval no. 13; 25 December 2025), and all participants provided verbal informed consent before inclusion; written consent was not used because the study was non-interventional and of minimal risk (see the Informed Consent Statement). Clinical trial registration was not required because no intervention was prospectively assigned and the study therefore does not meet the ICMJE definition of a clinical trial. The study was conducted in accordance with the Declaration of Helsinki. All procedures complied with the ethical standards of the institutional research committee and the Declaration of Helsinki and its subsequent amendments. The present report covers the insulin resistance and laboratory outcomes of the approved protocol. Hepatic steatosis outcomes are outside the scope of this report.

The 54 participants are also included in a separate article on hepatic and renal shear-wave elastography (HERMES; accepted for publication in Frontiers in Endocrinology), which has its own ethics approval; its imaging outcomes are not included in this report. HERMES also reports several of the laboratory measures analysed here, whereas HOMA-IR, the TyG index, FIB-4, the mixed-model and kidney-subgroup analyses of the insulin-resistance indices, the medication-based sensitivity analyses, and total cholesterol, HDL-C, LDL-C and serum albumin are not reported in it. HERMES analyses its imaging outcomes by its own kidney classification, which differs from the present one by one participant (Section 2.2). A further manuscript in preparation, on epicardial adipose tissue in the same source patient group, includes HOMA-IR values for 45 participants that overlap with the present data; its echocardiographic outcomes are not included in this report. The measures reported for the shared participants in the present report and in HERMES are compared in Table S11.

2.7. Data Quality Assurance

Clinical and laboratory data were collected prospectively using standardised institutional protocols. Laboratory measurements were performed in the same certified hospital laboratory throughout the study using routine quality-control procedures. Data completeness was verified before statistical analysis, and all analyses were conducted using complete-case data without imputation.

3. Results

3.1. Baseline Characteristics

A total of 54 participants completed the six-month follow-up and were included in the final analysis. The mean age was 61.8 ± 9.2 years, 31 participants (57.4%) were female,

and the median diabetes duration was 2.5 years (IQR 1.0–6.0). At baseline, 14 participants (25.9%) had eGFR <60 mL/min/1.73 m^2 and 40 (74.1%) had eGFR ≥60. Dapagliflozin was prescribed to 45 participants (83.3%), while 9 (16.7%) received empagliflozin. Insulin use was documented in 13 participants (24.1%) (basal in 8, basal-bolus in 3, premixed in 1 and regimen not recorded in 1); 45 (83.3%) used metformin; 25 (46.3%) used a DPP-4 inhibitor; 12 (22.2%) used pioglitazone; 5 (9.3%) used a sulfonylurea; and none used a GLP-1 receptor agonist. Hypertension was recorded in 30 participants (55.6%) and coronary artery disease in 2 (3.7%); none had a recorded history of heart failure, stroke or peripheral artery disease. The record form documented no change in non-insulin glucose-lowering agents during follow-up, except that the change field was unknown for three participants whose entries were overturned by record review. Continued use of the prescribed SGLT2 inhibitor was confirmed at the six-month visit by patient report and review of the prescription record, and no discontinuation was recorded; dispensing quantities were not available.

At baseline, participants had substantial insulin resistance, with a median HOMA-IR of 8.38 (IQR 3.47–13.26) and a median TyG index of 9.45 (IQR 9.16–9.99). Baseline demographic, clinical and biochemical characteristics are summarised in Table 1.

3.2. Longitudinal Metabolic Changes

Median HOMA-IR was 8.38 (IQR 3.47–13.26) at baseline, 3.37 (2.27–6.17) at month 3 and 3.14 (2.19–4.39) at month 6. The reduction in group medians was 62.6% (54 non-zero pairs; rank-biserial r = −0.79; BH-adjusted $p < 0.001$ within the 15-outcome family). Because insulin use was documented in 13 participants, these full-cohort HOMA-IR estimates are affected by exogenous insulin; analyses restricted to participants without documented insulin use are reported in Section 3.5. TyG decreased from 9.45 (9.16–9.99) to 9.10 (8.77–9.48) and 9.04 (8.76–9.38), respectively (−4.3%; r = −0.63; BH-adjusted $p < 0.001$). TyG requires no insulin measurement, but it is not independent of insulin therapy or of direct glucose lowering by SGLT2 inhibitors. Neither change alone establishes an improvement in insulin sensitivity.

Changes across the remaining metabolic variables are summarised in Table 2 and Figures 2–4. After Benjamini–Hochberg adjustment within the 15-variable metabolic family, significant baseline-to-6-month changes were observed for fasting insulin (−50.0%, r = −0.71), C-peptide (−33.2%, r = −0.61), fasting plasma glucose (−20.7%, r = −0.63), HbA1c (−2.0%, r = −0.51), triglycerides (−5.7%, r = −0.46), serum uric acid (−14.0%, r = −0.53) [35], gamma-glutamyl transferase (−17.5%, r = −0.41) and haemoglobin (+5.0%, r = +0.69). Changes in ALT (−7.5%), the FIB-4 index, eGFR (+2.8%), urinary albumin concentration and BNP did not reach significance after adjustment. The haemoglobin increase does not identify its mechanism and is not evidence of individual treatment adherence. Unadjusted and adjusted p values for all 15 variables are given in Table 2. The significance classification of the original 15 outcomes was unchanged in the expanded 17-comparison sensitivity analysis (Table S5). The five additional laboratory series showed no significant baseline-to-6-month change within their own five-test BH family (minimum q = 0.070; Table S8). In the 22-test sensitivity family, serum albumin decreased from a median of 42.0 to 41.0 g/L (q = 0.037), and the significance classification of the original 15 outcomes was unchanged (Table S9).

3.3. Relationship Between Change in HOMA-IR and Change in HbA1c

Change in HOMA-IR was not significantly correlated with change in HbA1c from baseline to month 6 (Spearman ρ = −0.15, nominal $p = 0.27$; Figure 5). A non-significant correlation in this sample does not establish independence or a glycaemia-independent

mechanism. This exploratory correlation remains subject to the limitations of HOMA-IR in participants using insulin.

In the pooled mixed model for all 54 participants, log-HOMA-IR was lower at month 3 ($\beta = -0.683$, SE 0.110; nominal $p < 0.001$) and month 6 ($\beta = -0.818$, SE 0.110; nominal $p < 0.001$), corresponding to multiplicative estimates of 0.50 and 0.44 relative to baseline. TyG was lower at month 3 ($\beta = -0.356$, SE 0.075) and month 6 ($\beta = -0.425$, SE 0.075; both nominal $p < 0.001$). These are unadjusted time associations. The pooled estimates are distinct from reference-group time coefficients in the separate exploratory kidney-interaction models. Full coefficients and diagnostics are provided in Table S4.

3.4. Exploratory Kidney Function Analyses

At baseline, 14 participants had eGFR <60 mL/min/1.73 m^2 and 40 had eGFR ≥60. Kidney subgroup analyses use these two groups only. Urinary albumin concentration was not used to define albuminuria categories. Descriptive changes, between-group comparisons, interaction models and trajectories are reported in Tables S2–S4 and Figure S1. These analyses are exploratory and cannot establish chronic kidney disease or a differential treatment effect.

3.5. Sensitivity Analyses Based on Medication Records and Insulin Thresholds

In the 41 participants without documented insulin use at baseline or month 6, median HOMA-IR decreased from 6.15 to 3.02 (−50.9%; r = −0.76; nominal $p < 0.001$) and TyG from 9.46 to 9.00 (−4.8%; r = −0.77; nominal $p < 0.001$; Table 3). Interim insulin exposure between these visits was not verified. Restricting the analysis further to the 39 participants with a documented absence of change in other glucose-lowering therapy gave a HOMA-IR decrease of 58.3% (r = −0.77) and a TyG decrease of 5.6%; two participants with an unknown change field were excluded. Restricting the analysis to the 40 participants without insulin in either source before record review gave similar results (HOMA-IR −54.9%; TyG −5.2%). In the 13 participants with documented insulin use, HOMA-IR cannot be interpreted as an index of insulin resistance and is shown descriptively only; their TyG did not change (+1.0%; nominal $p = 0.59$). Insulin doses and dose changes were not available, so insulin titration during follow-up could not be assessed. The exploratory exclusions above 100 or 50 μU/mL fasting insulin at any visit are retained for comparison (4 and 8 participants excluded; HOMA-IR −60.9% and −50.0%); fasting insulin concentrations cannot identify exogenous insulin use.

4. Discussion

In this prospective observational cohort, HOMA-IR and TyG decreased during six months of follow-up after SGLT2 inhibitor initiation. The reductions in group medians were 62.6% and 4.3%, respectively. Insulin use was documented in 13 participants; in the 41 without documented insulin use, HOMA-IR decreased by 50.9% and TyG by 4.8%. TyG avoids an insulin assay but is affected by glucose- and triglyceride-lowering treatment. Neither index provides independent confirmation of improved insulin sensitivity in this uncontrolled setting. Interim insulin exposure, insulin titration, weight and behaviour could not be assessed.

4.1. Magnitude of the Observed HOMA-IR Change in Context

Previous studies have evaluated changes in TyG and related atherogenic indices during SGLT2 inhibitor therapy [36,37], while a meta-analysis of randomised trials reported reductions in HOMA-IR and a clamp study reported improved skeletal-muscle insulin sensitivity [38,39]. The large HOMA-IR decrease in the present cohort should not be in-

terpreted as a larger drug effect: regression to the mean, insulin use in about a quarter of participants with possible dose titration, and within-person variation in fasting insulin may contribute. The percentage changes in HOMA-IR and TyG are also not directly comparable measures of biological response, because the indices have different formulas and TyG is logarithmically scaled. The magnitude of HOMA-IR change should therefore be interpreted cautiously.

4.2. Relationship Between Change in Insulin Resistance and Glycaemic Change

The non-significant change-score correlation ($\rho = -0.15$; nominal $p = 0.27$) does not establish a glycaemia-independent change in insulin resistance. Both scores contain measurement error, and HOMA-IR additionally depends on insulin therapy in participants receiving it. Direct insulin-sensitivity measurements, such as clamp-based assessment, would be required to test the physiological interpretation of these surrogate changes. The correlation reported here is descriptive.

4.3. Mechanistic Interpretation

SGLT2 inhibitors directly lower circulating glucose, which is a component of both HOMA-IR and TyG. By definition, $\Delta\text{TyG} = \Delta\ln(\text{glucose}) + \Delta\ln(\text{triglycerides})$. In the present dataset, the mean log changes were −0.222 and −0.203, respectively; the glucose term accounted arithmetically for 52.3% of the mean log-index decrease. This is a mathematical decomposition, not a causal attribution or a measure of improved insulin sensitivity. Experimental cardiac evidence suggests that SGLT2 inhibitors can activate PANK1 and coenzyme A synthesis [33], providing context for altered substrate metabolism without proving such a mechanism in this cohort. The observed haemoglobin increase is compatible with several mechanisms, including changes in plasma volume and erythropoiesis; neither was measured, and haemoglobin was not used as a surrogate for adherence.

Experimental studies have described protection against myocardial ischaemia–reperfusion injury [40] and improved myocardial energetics [41] with SGLT2 inhibitors, and direct renoprotective effects, including anti-inflammatory effects, have been reported in experimental kidney models [42]; sirtuin 1/peroxisome proliferator-activated receptor-γ coactivator 1α (SIRT1/PGC-1α) signalling is a general pathway of mitochondrial and metabolic control in muscle [43]. No inflammatory, mitochondrial or molecular markers were measured in this study, so these pathways cannot be linked to our observations and are mentioned only to indicate the mechanisms that a controlled study with appropriate biomarkers could test.

4.4. Interpretation of the Exploratory Subgroup Finding

Kidney subgroup results are reported mainly in the Supplementary Material. The previous urinary albumin-to-creatinine classification was invalid because the measured urine variable was albumin concentration in mg/L. Revised analyses compare baseline eGFR <60 ($n = 14$) with ≥60 ($n = 40$). The nominal month-6 TyG interaction was $p = 0.0015$ and the direct between-group change comparison was $p = 0.0125$. These unadjusted, post hoc findings concern a glucose-dependent index, in small groups without adjustment for background therapy; they do not establish differential insulin-sensitivity responses or a causal effect of renal function. HOMA-IR log-change differed with nominal $p = 0.424$. A single baseline eGFR does not establish chronicity.

4.5. Clinical Implications

These findings do not support changes in treatment or selection of TyG as a validated replacement for direct assessment of insulin sensitivity. They illustrate how indices can

change during routine care and why medication histories and the components of each index must be considered. Future controlled studies should verify insulin exposure, systematically record concomitant therapy and include direct physiological measures where feasible. Participants' awareness that their data were being studied could itself have changed adherence to medication, diet or physical activity; these behavioural changes were not measured.

4.6. Strengths of the Study

Strengths include prospective assessment at three scheduled time points and complete visit follow-up in the 54 included participants. Providing the de-identified data, variable dictionary and revised analysis script allows the reported laboratory summaries and revision analyses to be inspected and reproduced. Multiplicity control is explicit for the stated outcome families, while analyses outside those families are labelled exploratory. Background medication was abstracted from two record sources, and discordant entries were resolved by record review. Complete visit attendance, however, does not demonstrate uninterrupted drug use.

4.7. Limitations

The uncontrolled design precludes causal attribution, and regression to the mean may contribute to the observed changes. Body weight or BMI, blood pressure and smoking status were not recorded in the source records, so their confounding effects and the clinical representativeness of the cohort cannot be fully assessed. Background medication and comorbidities were abstracted from hospital and prescription records during revision rather than recorded on a study form at each visit; nine discordant entries between sources were resolved by record review. Insulin use was documented at baseline and month 6 only; interim exposure, doses and dose changes were not recorded, so insulin titration cannot be excluded as a contributor to HOMA-IR changes, and HOMA-IR is not interpretable as an insulin-resistance index in the 13 participants with documented insulin use; arbitrary fasting-insulin thresholds do not resolve that limitation. Continued use of the SGLT2 inhibitor was confirmed at the six-month visit by patient report and review of the prescription record, but dispensing dates and quantities were not available, so the proportion of days covered and day-to-day adherence could not be quantified; completion of visits and an increase in haemoglobin cannot substitute for these records. Awareness of study participation may have influenced behaviour. HOMA-IR and TyG were not the primary outcome of the approved protocol, and the outcome families and additional analyses were defined at the analysis or revision stage. The single-centre sample is small; kidney strata are especially imprecise and based on a single assessment. Reasons for non-enrolment of five screened patients were not available, and two enrolled participants (one lost to follow-up and one who declined the repeat examination) were not included in the analysis. Verbal consent was used under the present study protocol (approval no. 13), and no participant-signed consent documentation exists for this protocol, as disclosed to the editorial office. The analytical or calculation method used for LDL-C was not available. Six months is insufficient to evaluate long-term clinical outcomes. The urine measurement cannot establish albumin-to-creatinine categories because urinary creatinine was unavailable.

4.8. Clinical Perspective

The findings should be tested in a controlled study with a comparator arm (active comparators such as GLP-1 receptor agonists being one option [44]), systematic capture of weight, blood pressure, diet, activity and concomitant medication, verified medication records permitting valid use of insulin-based indices, and a follow-up long enough for clinical outcomes.

4.9. Future Directions

Building on the findings reported here, future multicentre randomised studies with longer follow-up, body-composition analyses, continuous glucose monitoring, and verified medication records are needed to confirm the metabolic response and to determine whether early changes in insulin resistance indices during SGLT2 inhibitor therapy predict long-term cardiovascular and renal outcomes. Such prognostic value cannot be assumed: in a separate myocardial-infarction cohort, TyG was associated with in-hospital death, but the indices had limited predictive value for 12-month major adverse cardiac and cerebrovascular events [45].

4.10. Take-Home Message

HOMA-IR and TyG decreased during follow-up after SGLT2 inhibitor initiation, including in participants without documented insulin use, but direct changes in index components, the lack of insulin-dose records and the uncontrolled design prevent interpretation as a confirmed improvement in insulin sensitivity or a treatment effect.

5. Conclusions

In this uncontrolled six-month observational cohort, HOMA-IR and TyG decreased after SGLT2 inhibitor initiation, and HOMA-IR also decreased in the 41 participants without documented insulin use. TyG requires no insulin measurement but can change directly with glucose- and triglyceride-lowering treatment. Neither result establishes improved insulin sensitivity or an effect attributable to SGLT2 inhibition. The findings are exploratory and require confirmation in controlled studies with prospectively recorded medication histories, systematic measurement of confounders and direct assessment of insulin sensitivity.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijtm6040052/s1, a data and code archive containing Data S1 (de-identified participant-level dataset for the primary analyses); Data S1b (additional laboratory series); Data S1c (medication, comorbidity and diabetes duration); Table S1 (variable dictionary for all three data files); and Script S1 (revised reproducibility script); and a document of supplementary revision analyses containing renal strata (Table S2), kidney-group change comparisons (Table S3), pooled and kidney-interaction models with diagnostics (Table S4), expanded 17-test BH sensitivity analysis (Table S5), all six visit-pair comparisons (Table S6), illustrative future sample-size scenarios (Table S7), additional laboratory series (Table S8), 22-test BH sensitivity analysis (Table S9), source discordances resolved by record review (Table S10), measures reported for the shared participants in the present report and in HERMES (Table S11) and kidney-group trajectories (Figure S1).

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Health Sciences Research Ethics Committee of Osmaniye Korkut Ata University (approval number: 13; meeting number: 12; date: 25 December 2025). Clinical trial registration was not required because the study was non-interventional: the SGLT2 inhibitor was started by the treating physician in routine care, before and independently of inclusion, and no intervention was assigned by the investigators.

Informed Consent Statement: Consent was verbal. Verbal informed consent was obtained from every participant before inclusion, at the outpatient visit at which the treating physician initiated the SGLT2 inhibitor; written consent was not obtained, and no signed consent form exists under the present study

protocol (approval no. 13). The study protocol approved by the Health Sciences Research Ethics Committee of Osmaniye Korkut Ata University (approval number 13, 25 December 2025) required that informed consent be obtained but did not stipulate whether it should be written or verbal, and the approval document does not specify a form of consent. All 54 participants gave verbal consent, which is the form actually obtained. The investigators considered verbal consent proportionate because the study was non-interventional and of minimal risk: it recorded only measurements obtained in routine clinical care, added no intervention, procedure, visit or additional risk, and the analysis dataset contains no directly identifying information. No written script was used when consent was obtained; a signed attestation, prepared subsequently, of the information provided to participants has been supplied to the editorial office. The absence of documented written consent is acknowledged as a limitation of the study records.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

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