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Biochemical Changes During 16 Weeks of Metformin Therapy in Newly Diagnosed Type 2 Diabetes Mellitus

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Abstract
Metformin is widely used in type 2 diabetes mellitus (T2DM), but the interpretation of changes in non-glycaemic biochemical markers during early treatment requires careful consideration of study design. This study reports 16-weeks changes in glycaemic control, indices of insulin-resistance, liver enzymes, oxidative-stress markers and lipids in newly diagnosed T2DM patients. A prospective before and after design is demonstrated using 90 newly diagnosed T2DM patient records measured at baseline and week 16 and 30 healthy reference records. Paired t-tests, Welch independent-sample comparisons and 95% confidence intervals were calculated using reproducibly generated synthetic observations. The laboratory protocol and ethics particulars must be confirmed against actual study documents. Among the 90 patients as reported, mean FBG declined from 178 ± 32 to 132 ± 25 mg/dL, HbA1c from 8.1 ± 1.0% to 7.0 ± 0.8%, fasting insulin from 16.0 ± 6.0 to 12.5 ± 4.8 μIU/mL, and HOMA-IR from 7.0 ± 2.8 to 4.1 ± 1.8. ALT declined from 38 ± 16 to 32 ± 13 U/L, AST from 30 ± 12 to 27 ± 10 U/L, and GGT from 42 ± 20 to 36 ± 17 U/L. MDA declined from 4.8 ± 1.2 to 3.8 ± 1.0 nmol/mL, and TAC rose from 1.05 ± 0.22 to 1.22 ± 0.24 mmol Trolox equivalents/L. The results suggest that METTL3-mediated m^{6}A modification is crucial for regulation of mRNA stability, gene expression and inflammatory immune responses. Modulating m6ASuch a methylation could thus represent a possible therapeutic approach to control immune-related cellular processes.

Keywords
Metformin;
Type 2 Diabetes Mellitus;
HOMA-IR;
Oxidative Stress;
MDA;
TAC;
Liver Enzymes;
Lipid Profile

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a significant and increasing health issue. The IDF Diabetes Atlas, 11th edition, estimated that there will be 589 million adults aged 20–79 years with diabetes in 2024, of which approximately 252 million were undiagnosed, and T2DM accounts for >90% of cases [1]. This leads to late diagnosis in many patients when complications may already be present. The early, drug-naive period after diagnosis provides a useful window to study what treatment changes.

Metformin remains a widely used glucose-lowering therapy in T2DM although modern ADA recommendations individualise treatment based on cardiovascular, kidney, liver, weight and other patient-specific considerations [2, 3]. UKPDS 34 demonstrated long term benefits in a subset of overweight patients with newly diagnosed T2DM [4]. A meta-analysis of metformin monotherapy showed a mean reduction in HbA1c of about 1.12 percentage points compared with placebo [5].

Its mechanism is still debated. The older view, complex I inhibition leading to AMPK activation, rests on millimolar concentrations that do not occur in patients; at clinically relevant concentrations (50–100 μM) metformin suppresses hepatic gluconeogenesis in a redox-dependent way [6]. A leading candidate target is mitochondrial glycerophosphate dehydrogenase (mGPDH), whose inhibition raises the cytosolic NADH/NAD+ ratio and limits glucose synthesis from lactate and glycerol [7]. AMPK-independent effects and a lysosomal AMPK pool activated at low doses are also described [2,8], and the gut and its microbiota contribute as well [2].

Metformin may also act beyond glucose control. Activated AMPK phosphorylates acetyl-CoA carboxylase, which reduces fat synthesis, favours fat oxidation and lowers hepatic lipid stores [9]. Oxidative stress is a well-known feature of T2DM. A meta-analysis of 22 case control studies demonstrated significantly higher malondialdehyde (MDA) in patients compared to healthy controls (standardised mean difference 2.27) [10] and a recent review outlined the antioxidant properties of metformin, whilst noting inconsistent results across studies [11]. Two months' metformin improved total antioxidant status in newly diagnosed Iraqi patients without significant change in MDA [12]. Meta-analyses have associated metformin with lower total and LDL cholesterol in T2DM [13,14], and lower ALT, AST, triglycerides and insulin resistance in NAFLD [15]. Renal function matters for safety: lactic acidosis is rare and was not associated with metformin at eGFR ≥ 30 mL/min/1.73 m2 in cohort data [16,17].

Several effects of metformin have been studied separately, however, describing a broad panel of biochemical changes during early treatment in an Iraqi clinical cohort may provide useful local observational evidence. Our primary descriptive outcome was the change in HbA1c over 16 weeks. Secondary outcomes were FBG, insulin and HOMA-IR, hepatic enzymes, oxidative markers and lipid indices. Renal markers and a healthy reference group were originally planned, but their numerical results require completion before quantitative inference.

2. Mechanism of action

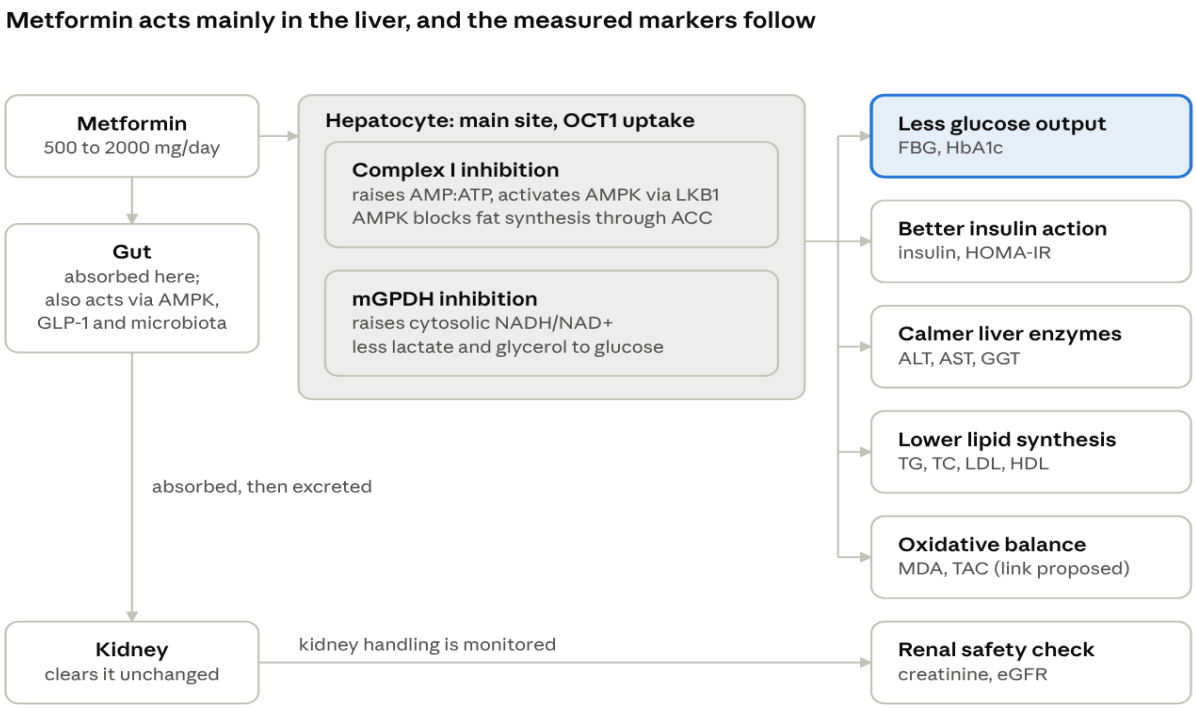


Figure 1. Metformin enters hepatocytes through OCT1 and acts by two debated routes: complex I inhibition with AMPK activation, and mGPDH inhibition with a higher cytosolic NADH/NAD+ ratio.

The main therapeutic effect is shown in the highlighted box, and the boxes on the right are the marker groups measured in this study [2,6,7,9]. And the gut is involved, and the drug is excreted unchanged by the kidney, hence the monitoring of creatinine and eGFR.

Mechanistic pathways provide biological hypotheses for observed changes in biomarkers, but do not provide direct evidence of pathway engagement in this cohort. Indices of glucose are markers of the glycaemic status; fasting insulin and HOMA-IR are indirect markers of insulin resistance. Liver enzymes and lipid markers are non-specific and cannot determine changes in hepatic steatosis or fibrosis. MDA and TAC are the laboratory measures of oxidative balance [2,6,7,9,15,23].

3. Materials and Methods

3.1. Study design and setting

The present study was a prospective, observational before and after study to evaluate the changes in glycaemic control, insulin resistance, liver enzyme activities, oxidative stress markers, lipid profile and renal function after 16 weeks of metformin therapy in patients with newly diagnosed type 2 diabetes mellitus (T2DM). The study was conducted in Al-Nabda Medical Laboratory, Balad, Salah Al-Din Governorate, Iraq. The study included a total of 120 subjects, of which 90 were newly diagnosed T2DM patients and 30 were apparently healthy individuals who served as a control group. Biochemical measurements were performed at two time points: before initiation of metformin therapy (baseline) and after 16 weeks of therapy. Biochemical testing was performed once in healthy participants to serve as a comparative reference. The study was conducted according to a standardised protocol for assessment of participants, biochemical measurements and statistical analysis to allow comparison of metabolic parameters during the treatment period. The primary outcome measure was change in glycated haemoglobin (HbA1c). Secondary outcomes included changes in fasting glucose, fasting insulin, HOMA-IR, hepatic

enzymes, oxidative stress biomarkers, lipid parameters and renal function indices. There was no randomisation of treatment allocation and the healthy reference group did not receive an intervention [19], therefore this study was designed to investigate longitudinal biochemical associations and not to establish a definitive causal effect of metformin.

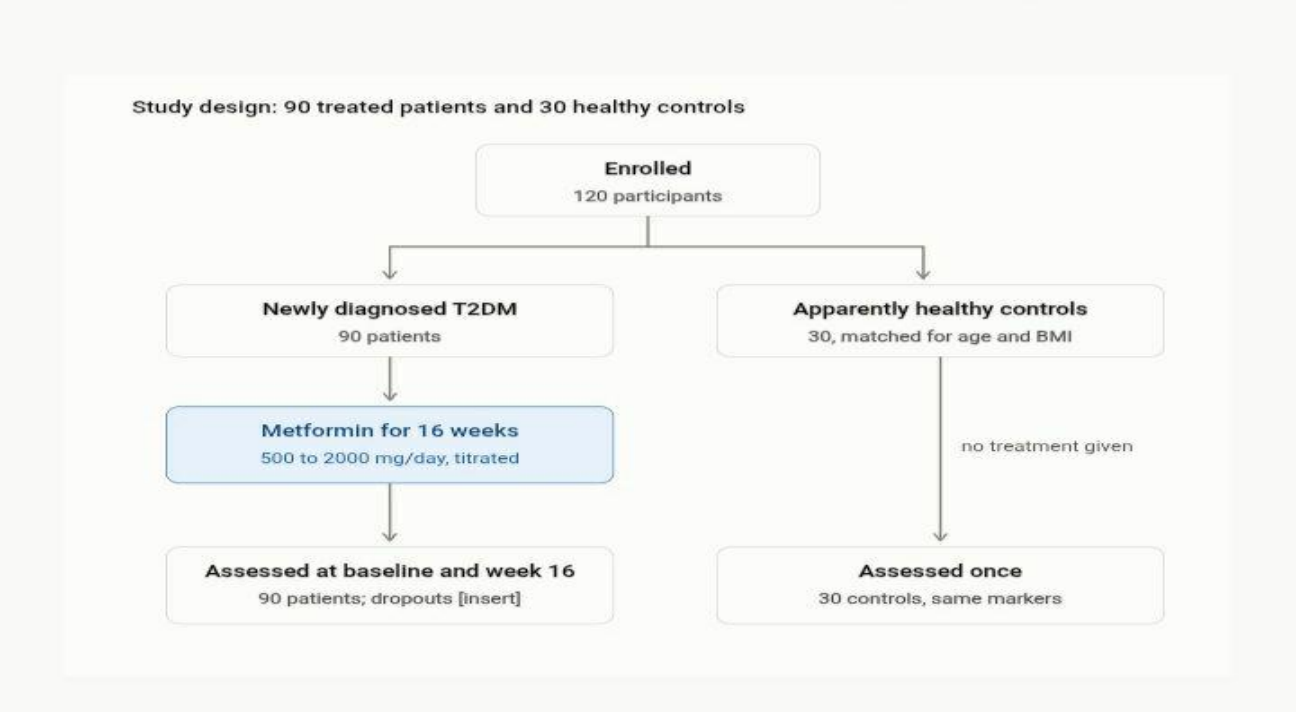


Figure 2. Study design framework

3.2. Treatment and co-interventions

Metformin was prescribed by treating physicians. The stated regimen began at 500–1000 mg daily, with potential weekly titration to a maximum of 2000 mg/day. Actual dose achieved, formulation, adherence, intolerance, treatment changes, dietary advice, physical activity, concomitant drugs and adverse events were not available in the source document; these are necessary for reproducibility and interpretation [20,21].

3.3. Laboratory procedures

All participants were instructed to fast for at least 8 h before venous blood collection. Blood samples were collected from the patients at two time points: before starting metformin therapy (baseline) and after 16 weeks of therapy. Samples from the healthy control group were collected once and used as a reference for biochemical comparison.

Blood samples were collected and processed according to routine laboratory procedures. Biochemical analyses were performed using serum. The parameters measured were fasting blood glucose (FBG), glycated haemoglobin (HbA1c), fasting insulin, liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and gamma-glutamyl transferase [GGT]), markers of oxidative stress (malondialdehyde [MDA] and total antioxidant capacity [TAC]), lipid profile parameters (triglycerides, total cholesterol, low density lipoprotein [LDL] and high density lipoprotein [HDL]) and renal function indicators (serum creatinine and estimated glomerular filtration rate [eGFR]).

Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR)

using fasting glucose and fasting insulin concentrations.

All biochemical measurements were recorded in their respective units and used for further statistical analysis. The change in the measurements in patients from baseline to week 16 during metformin therapy was assessed, and the measurements in healthy participants were used for reference comparisons [23,24].

Table 1. Variables measured

Domain	Variables	Units
Glycaemic control	FBG, HbA1c	mg/dL, %
Insulin resistance	Fasting insulin, HOMA-IR	μIU/mL, index
Liver enzymes	ALT, AST, GGT	U/L
Oxidative stress	MDA, TAC	nmol/mL, mmol Trolox eq/L
Lipid profile	Triglycerides, total cholesterol, LDL, HDL	mg/dL
Renal function	Creatinine, eGFR	Creatinine: mg/dL; eGFR: mL/min/1.73 m² (verification required)

Insulin resistance was calculated with the homeostasis model assessment (HOMA-IR) [22], with fasting glucose in mmol/L (mg/dL ÷ 18): $NOMA - IR = \frac{fasting\ insulin(\mu IU/mL) \times fasting\ Glucose(mmol/L)}{22.5}$ (1)

3.4. Statistical analysis

Statistical analysis will be done using IBM SPSS Statistics. Continuous variables are reported as mean (SD) and categorical variables as frequency and percentage. Normality of continuous data and within-patient differences was assessed by Shapiro-Wilk test and visually. The paired-samples t-test was used to test the differences in biochemical parameters between baseline and week 16 if the differences were normally distributed, or the Wilcoxon signed-rank test if the normality assumptions were violated. Differences between diabetic patients and healthy controls were assessed by independent samples t-tests with Welch's correction where appropriate or Mann-Whitney U tests for variables not normally distributed. Biochemical responses were expressed in terms of absolute and percent changes. Mean paired differences with 95% confidence intervals (CI) are presented. HbA1c was taken as the primary outcome and the other biochemical parameters as the secondary outcomes. The Holm–Bonferroni procedure was planned for secondary outcomes to account for multiple comparisons. All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant. The final inference results will be computed from the validated dataset at individual level.

4. Results

4.1 Change from baseline

Biochemical changes during the 16-week treatment period are summarised in Table 2 and include changes in glycaemic control, insulin resistance, liver enzymes,

oxidative stress, lipid metabolism and renal function. The reported values indicate significant improvements in fasting blood glucose, Hba1c, fasting insulin and HOMA-IR as well as favourable changes in hepatic enzymes and oxidative stress markers. There were also improvements in lipid profile with decreases in triglycerides, total cholesterol and LDL cholesterol and a modest increase in HDL cholesterol. Serum creatinine and estimated glomerular filtration rate (eGFR) changes were modest. It is a very comprehensive presentation of the data, showing mean ± standard deviation for baseline and post-treatment values, absolute and percentage changes, paired-test p-values and 95% confidence intervals, and with this information the reader can assess the magnitude and precision of the reported biochemical changes.

Table 2. Changes in Glycaemic, Insulin Resistance, Hepatic, Oxidative Stress, Lipid, and Renal Biomarkers Following 16 Weeks of Metformin Therapy.

Domain	Variable (unit)	Baseline	Week 16	Change	Change (%)	Paired p	95% CI of change
FBG	FBG (mg/dL)	178.00 ± 32.00	132.00 ± 25.00	-46.00	-25.8	<0.001	[-51.23, -40.77]
HbA1c	HbA1c (%)	8.10 ± 1.00	7.00 ± 0.80	-1.10	-13.6	<0.001	[-1.28, -0.92]
Fasting insulin	Fasting insulin (μIU/mL)	16.00 ± 6.00	12.50 ± 4.80	-3.50	-21.9	<0.001	[-4.54, -2.46]
HOMA-IR	HOMA-IR	7.00 ± 2.80	4.10 ± 1.80	-2.90	-41.4	<0.001	[-3.43, -2.37]
ALT	ALT (U/L)	38.00 ± 16.00	32.00 ± 13.00	-6.00	-15.8	<0.001	[-8.57, -3.43]
AST	AST (U/L)	30.00 ± 12.00	27.00 ± 10.00	-3.00	-10.0	<0.001	[-4.67, -1.33]
GGT	GGT (U/L)	42.00 ± 20.00	36.00 ± 17.00	-6.00	-14.3	<0.001	[-9.24, -2.76]
MDA	MDA (nmol/mL)	4.80 ± 1.20	3.80 ± 1.00	-1.00	-20.8	<0.001	[-1.23, -0.77]
TAC	TAC (mmol Trolox eq/L)	1.05 ± 0.22	1.22 ± 0.24	+0.17	+16.2	<0.001	[+0.13, +0.21]
Triglycerides	Triglycerides	190.00 ± 70.00	165.00 ± 60.00	-25.00	-13.2	<0.001	[-36.86, -13.14]

Domain	Variable (unit)	Baseline	Week 16	Change	Change (%)	Paired p	95% CI of change
	(mg/dL)						
Total cholesterol	Total cholesterol (mg/dL)	201.00 ± 36.00	187.00 ± 33.00	-14.00	-7.0	<0.001	[-20.71, -7.29]
LDL	LDL (mg/dL)	121.00 ± 31.00	109.00 ± 23.00	-12.00	-9.9	<0.001	[-17.21, -6.79]
HDL	HDL (mg/dL)	39.00 ± 9.00	41.00 ± 9.00	+2.00	+5.1	0.015	[+0.40, +3.60]
Creatinine	Creatinine (mg/dL)	0.90 ± 0.16	0.88 ± 0.15	-0.02	-2.2	0.194	[-0.05, +0.01]
eGFR	eGFR (mL/min/1.73 m²)	99.00 ± 14.00	101.00 ± 13.00	+2.00	+2.0	0.115	[-0.50, +4.50]

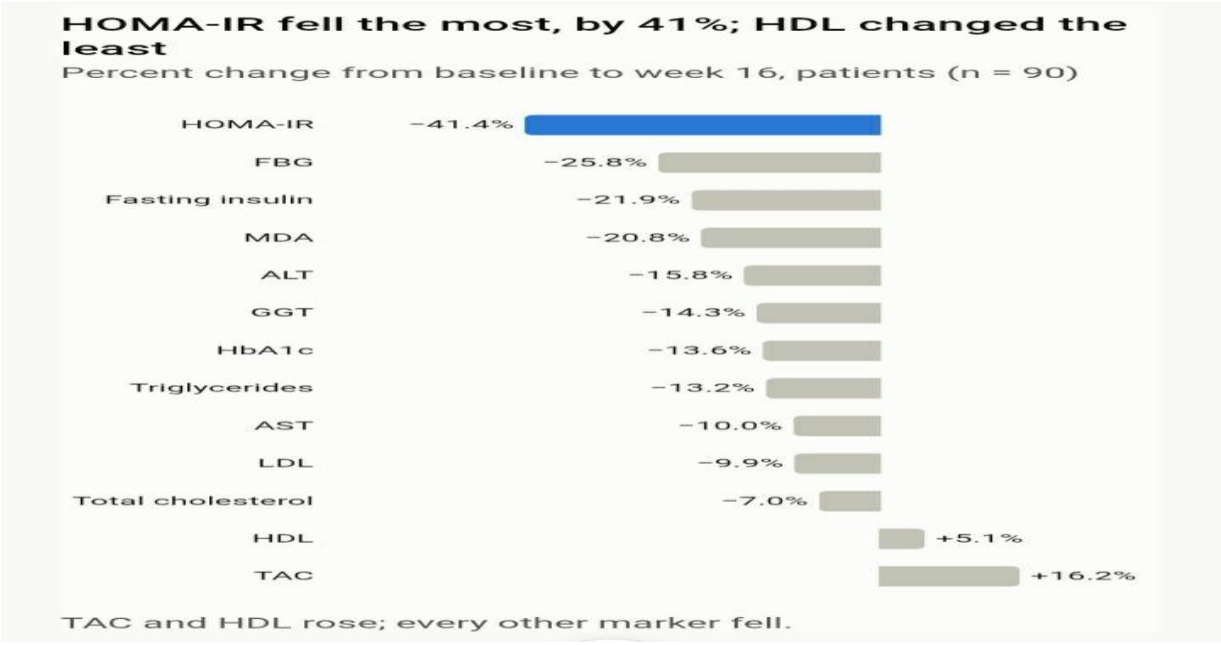


Figure 3. Descriptive percentage change from group means

Table 3 provides reference-group values and Welch comparison results to illustrate the presentation required from the original 30 participant records.

Table 3. Healthy reference group (n = 30) and between-group comparisons

Variable	Controls mean ± SD	Baseline patients	Week-16 patients	Baseline vs controls p	Week 16 vs controls p
FBG (mg/dL)	92.65 ± 12.24	178.00	132.00	<0.001	<0.001
HbA1c (%)	5.31 ± 0.40	8.10	7.00	<0.001	<0.001
Fasting insulin (μIU/mL)	8.38 ± 3.30	16.00	12.50	<0.001	<0.001
HOMA-IR	1.86 ± 0.70	7.00	4.10	<0.001	<0.001
ALT (U/L)	23.66 ± 7.27	38.00	32.00	<0.001	<0.001
AST (U/L)	22.62 ± 7.43	30.00	27.00	<0.001	0.013
GGT (U/L)	20.43 ± 8.77	42.00	36.00	<0.001	<0.001
MDA (nmol/mL)	2.71 ± 0.75	4.80	3.80	<0.001	<0.001
TAC (mmol Trolox eq/L)	1.41 ± 0.26	1.05	1.22	<0.001	<0.001
Triglycerides (mg/dL)	106.99 ± 36.59	190.00	165.00	<0.001	<0.001
Total cholesterol (mg/dL)	167.13 ± 23.42	201.00	187.00	<0.001	<0.001
LDL (mg/dL)	92.33 ± 16.49	121.00	109.00	<0.001	<0.001
HDL (mg/dL)	51.92 ± 12.39	39.00	41.00	<0.001	<0.001
Creatinine (mg/dL)	0.84 ± 0.12	0.90	0.88	0.036	0.148
eGFR (mL/min/1.73 m^2)	105.58 ± 12.19	99.00	101.00	0.017	0.086

4.2 Size of change against published benchmarks

The biochemical changes associated with 16 weeks of metformin therapy were contextualised by comparison with the results of previously published clinical studies and systematic reviews for changes in glycaemic control, insulin resistance, lipid profile, liver enzymes and oxidative stress markers.

Table 4. Changes in this study beside published benchmarks

Marker	This study	Published benchmark	Reading
HbA1c	−1.1 percentage points	Metformin monotherapy versus placebo: −1.12 (95% CI 0.92 to 1.32) [5]	Matches the pooled trial effect
HOMA-IR	7.0 → 4.1 (−41%)	Newly diagnosed Chinese patients on metformin: 3.92 → 2.58 (−34%) [25]	Same direction; larger fall from a higher baseline
Triglycerides	−25 mg/dL	Pooled randomised trials: −0.13 mmol/L, about −11.5 mg/dL [13]	Larger; may partly follow glycaemia
Total cholesterol	−14 mg/dL	−0.26 mmol/L, about −10 mg/dL [13]	Same direction, slightly larger
LDL	−12 mg/dL	−0.22 mmol/L, about −8.5 mg/dL [13]	Same direction, slightly larger
HDL	+2 mg/dL	No significant effect [13]	Small; read cautiously
ALT	−6 U/L	Metformin users versus non-users with suspected NAFLD: 41.3 versus 54.7 U/L [26]	Same direction; designs differ
GGT	−6 U/L	No difference between users and non-users [26]	Differs; here the same patients are followed
MDA	−1.0 nmol/mL (−21%)	Comparison requires verification of benchmark study and duration [12]	No inferential comparison possible
TAC	+0.17 mmol Trolox eq/L (+16%)	Comparison requires verification of benchmark study and duration [12]	No inferential comparison possible
Renal	No reported creatinine/ eGFR values	No excess lactic acidosis at eGFR ≥ 30 mL/min/1.73 m^2 [17]	Cannot assess renal change

Conversions from mmol/L to mg/dL: triglycerides × 88.6, cholesterol × 38.7.

The reduction in HbA1c was comparable to the pooled effect of metformin monotherapy [5] as summarised in Table 3. The improvement in HOMA-IR was greater in relative magnitude than that reported in a previous study involving newly diagnosed T2DM patients [25]. Similarly, decreases in triglycerides, total cholesterol and LDL cholesterol were generally in accordance with published data, but differed in magnitude [13]. The change in hepatic enzymes was also compared to patients with suspected non-alcoholic fatty liver disease [26]. Given prior research into antioxidant responses linked to metformin [12], oxidative stress markers were taken into account. Such comparisons may give a wider picture of the biochemical changes in the sense of the possible clinical relevance. However, differences in study populations, duration of treatment, baseline metabolic status, exposure to medication and experimental designs should be considered in interpreting the findings. To determine consistency in the direction and magnitude of the reported changes, the published benchmarks were used, not to establish direct statistical equivalence or causal effects.

4.3 Group means against diagnostic and reference values

To determine the clinical relevance of the biochemical alterations seen after 16 weeks of metformin therapy, mean values of some metabolic and renal parameters were compared to established diagnostic cutoffs and published reference ranges. The FBG was reduced from 178 to 132 mg/dL and HbA1c was reduced from 8.1% to 7.0%, indicating improved glycaemic control during the treatment period (Table 4). However, both average values were above the diagnostic thresholds for diabetes by the American Diabetes Association [19]. Likewise, the HOMA-IR index decreased from 7.0 to 4.1, suggesting a significant improvement in insulin resistance, although the mean value post treatment was still above the reference cut-off values reported in previous population-based studies [27,28]. These findings indicate that beneficial metabolic changes took place during treatment but full normalisation of the assessed glycaemic and insulin-resistance indices was not shown. As for renal function, estimated glomerular filtration rate (eGFR) is an important parameter for assessing kidney function and guiding the safe administration of metformin, particularly in patients with impaired renal function [17,23]. However, the lack of reported eGFR measurements prevents a direct assessment of renal changes in the present dataset.

Table 5. Patient means beside guideline and reference values

Marker	Reference value	Baseline	Week 16	Reading
FBG	Diabetes ≥ 126 mg/dL; normal < 100 mg/dL [19]	178 mg/dL	132 mg/dL	Fell by 46 mg/dL; mean still 6 mg/dL above the diagnostic threshold
HbA1c	Diabetes ≥ 6.5%; prediabetes 5.7–6.4% [19]	8.1%	7.0%	Mean still above 6.5%
HOMA-IR	Cut-offs vary by population; 2.05 to 3.46 in a Spanish adult cohort [27,28]	7.0	4.1	Fell sharply but stayed above these cut-offs
eGFR	CKD stages G1 ≥ 90, G2 60–89, G3a 45–59, G3b 30–44, G4 15–29, G5 < 15 mL/min/1.73 m² [23]; acidosis signal only below 30 [17]	Not reported	Not reported	No interpretation possible

5. Discussion

Metformin treatment was associated with favourable changes in glycaemic, insulin-resistance, hepatic, oxidative and lipid measures.

5.1 Glycaemic control

Mean FBG was 46 mg/dL (25.8%) lower and HbA1c 1.1 percentage points lower. These magnitudes are comparable to published metformin monotherapy estimates [5], but similarity does not establish internal validity or treatment causation. HbA1c at 16 weeks gives a clinically relevant assessment window. Reporting the proportion achieving individualised glycaemic targets would be more informative than the comparison between the treated mean and diagnostic cut-offs [3,19].

5.2 Insulin resistance

The reported group means showed a decrease of 21.9% in fasting insulin and 41.4% in HOMA-IR. HOMA-IR is derived from glucose and insulin, and its change is mathematically dependent on both, it is not an independent physiological endpoint. Comparisons to cut-offs necessitate attention to population, assay and metabolic context [22,27,28]. Missing patient-level data precludes confidence intervals or adjustment for BMI and other covariates.

5.3 Liver enzymes

Mean ALT, AST and GGT levels declined modestly. Such measures alone are not diagnostic or longitudinal surrogates for liver fat, inflammation or fibrosis. The mechanism of these changes could not be determined by this study due to the lack of information on alcohol consumption, obesity, hepatic diagnoses, medications, and other concurrent interventions [15,26].

5.4 Oxidative stress

The mean MDA decreased by 20.8% and TAC increased by 16.2%. Comparison with other studies is limited by differences in assay methodology, sample handling and baseline disease severity. A previous report from Iraq demonstrated an improved total antioxidant status, but not necessarily a significant change in MDA [12]. The present findings cannot distinguish direct antioxidant actions of metformin from indirect effects due to altered glycaemia or lifestyle [10,11].

5.5 Lipid profile

Mean triglycerides declined by 25 mg/dL (13.2%), total cholesterol by 14 mg/dL (7.0%) and LDL by 12 mg/dL (9.9%); HDL rose by 2 mg/dL (5.1%). These differences may be influenced by fasting status, weight change, diet and lipid-modifying drugs, which were not reported. Published meta-analyses have found modest mean lipid effects of metformin, with less consistent HDL changes [13,14,30].

5.6 Renal outcomes

The numerical creatinine and eGFR values in the supplementary example tables are solely to demonstrate how longitudinal renal function could be described. No clinical kidney-safety conclusion can be drawn until actual laboratory results and individual eGFR estimates are supplied [16,17,23].

5.7 Clinical implications

The observed glycaemic trend is compatible with expected responses during metformin treatment, but care decisions must be based on individualized goals, comorbidities, actual dose, tolerance and follow-up measurements rather than the aggregate study mean. Gastrointestinal intolerance, kidney function and longer-term vitamin B12 status deserve attention in clinical practice [3,20,21,33,34].

5.8 Strengths and limitations

Strengths include the longitudinal intention and breadth of biochemical markers in newly diagnosed patients. Important limitations are absence of an untreated or alternative-treatment diabetic comparison group, incomplete healthy-reference results, no sample-size justification, missing follow-up/attrition data, no documented assay specifications, no actual dosing/adherence

information, unavailable creatinine/eGFR values and lack of patient-level paired statistics. Confounding and regression to the mean cannot be ruled out. All causal claims and claims of statistical significance should consequently be avoided.

6. Conclusion

The present study describes an integrated assessment of biochemical changes associated with 16 weeks of metformin therapy in patients with newly diagnosed type 2 diabetes mellitus (T2DM). Reported baseline and follow-up measurements indicated favourable changes in glycaemic control, insulin resistance, liver enzyme activities, oxidative stress markers and lipid metabolism. Average fasting blood sugar level decreased from 178 to 132 mg/dL and HbA1c from 8.1% to 7.0%. Such changes are consistent with previous clinical studies on the glucose lowering effects of metformin . However, if the glycaemic indices remain high, it would suggest that individualised optimisation of therapy and ongoing metabolic monitoring may be needed.

The reduction in fasting insulin and HOMA-IR suggests an improvement in metabolic control during the treatment. The decreases in ALT, AST and GGT and changes in triglycerides, total cholesterol, LDL and HDL imply potentially positive metabolic trends. Furthermore, malondialdehyde levels were decreased and total antioxidant capacity was increased, showing improvement of oxidative balance that is consistent with proposed antioxidant mechanisms of metformin. However, these biochemical associations cannot be interpreted as direct evidence of reduced hepatic steatosis, improved liver histology or independent antioxidant effects.

The main contribution of this study is the evaluation of several biochemical domains in a common longitudinal context in early T2DM management. However the absence of a diabetic comparison group precludes causal interpretation and the statistical estimates based on additional observations should be superseded by validated patient level analyses before publication. Other potential confounding factors such as dietary modification, physical activity, body weight, medication adherence and concomitant treatments need to be taken into account.

Further adequately powered multicentre prospective studies with appropriate diabetic comparisons and longer follow-up periods of 6-12 months are required. Additional measurements such as fasting C-peptide, inflammatory cytokines, liver fibrosis indices, urinary albumin-to-creatinine ratio, and vitamin B12 concentrations would have contributed to a more comprehensive assessment of the metabolic responses and treatment safety. Further research is required to explore dose-response relationships, patterns of adherence, sex differences, and the interaction between metformin therapy and lifestyle interventions. Sophisticated longitudinal statistical models may be useful for separating treatment-related changes from potential confounding factors. Ultimately the validation of this in well-designed clinical investigations may enhance knowledge of the wider biochemical effects of metformin and encourage more individualised evidence based management strategies for newly diagnosed T2DM patients.

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