AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

EXPERIMENTAL EVALUATION OF THE EFFECT OF GLP-1 AGONIST AND METFORMIN COMBINATION ON INSULIN RESISTANCE IN A METABOLIC SYNDROME MODEL

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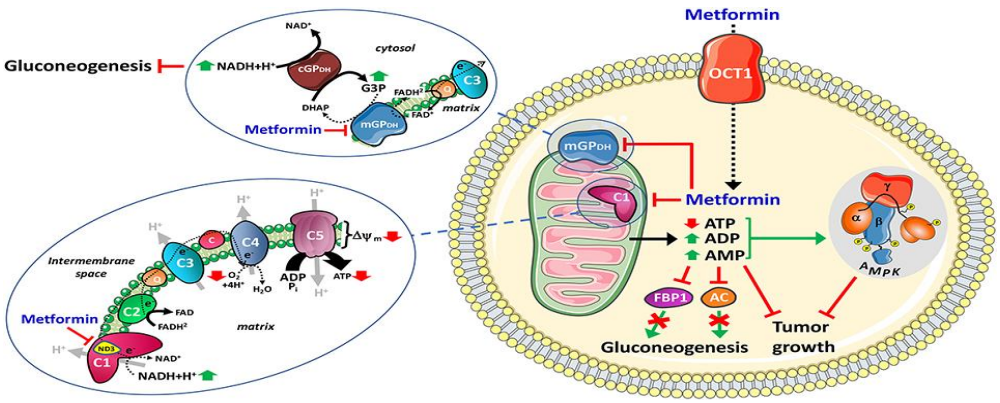
ABSTRACT: This study experimentally evaluated the effects of a GLP-1 agonist (liraglutide) and metformin, administered separately and in combination, on insulin resistance, glucose tolerance, body weight, and metabolic parameters in a metabolic syndrome (MetS) model. A 12-week high-fat/fructose diet was used to induce MetS, followed by a 4-week pharmacological intervention. The combination of GLP-1 RA + metformin demonstrated a pronounced improvement in OGTT outcomes, a marked reduction in the HOMA-IR index, decreased body weight, regression of hepatic steatosis, and lowered oxidative stress markers. The combined therapy achieved stronger restoration of insulin sensitivity compared to monotherapy with either agent. The findings indicate that GLP-1 RA and metformin exhibit a potent synergistic therapeutic potential when used together for treating metabolic syndrome.

Keywords: GLP-1 agonist, metformin, insulin resistance, metabolic syndrome, OGTT, HOMA-IR, hepatic steatosis.

INTRODUCTION

Metabolic syndrome (MetS) is a complex metabolic disorder characterized by abdominal obesity, insulin resistance, dyslipidemia, and arterial hypertension, all of which significantly increase the risk of developing type 2 diabetes and cardiovascular diseases [1–4]. The rising global prevalence of MetS underscores the need for deeper investigation into its pathogenesis, prevention, and modern therapeutic strategies [5–7]. Insulin resistance is a central pathogenic component of MetS.



In recent years, two major classes of drugs—GLP-1 receptor agonists (GLP-1 RA) and metformin—have been extensively studied and clinically validated for the management of MetS-related metabolic dysfunction [8–10]. Metformin enhances insulin sensitivity, reduces gluconeogenesis, and activates AMPK. GLP-1 RAs enhance glucose-dependent insulin secretion, reduce glucagon release, suppress appetite, and promote weight loss [11–14].

AMERICAN ACADEMIC PUBLISHER
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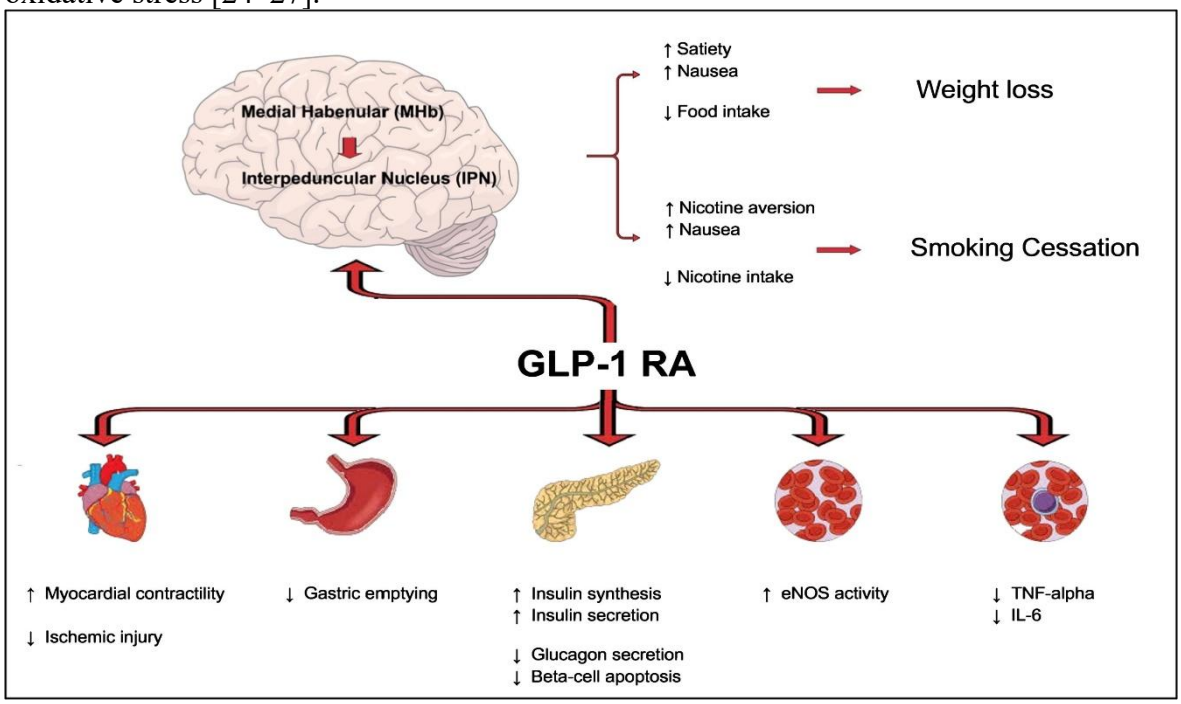
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Although the combination of metformin and GLP-1 RA is widely used in clinical practice, their experimental evaluation—particularly their synergistic effects on insulin resistance within a metabolic syndrome model—remains insufficiently studied [15–17]. These two agents target complementary molecular pathways: GLP-1 RAs act through the gut-brain-metabolism axis and the incretin system [18–20], whereas metformin primarily modulates hepatic glucose production and peripheral insulin sensitivity [21–23].

Therefore, combining these drugs may produce stronger therapeutic effects on the core pathogenic components of MetS: glucose homeostasis, body weight, lipid metabolism, and oxidative stress [24–27].



This study aimed to experimentally evaluate the effect of combined GLP-1 RA (liraglutide) and metformin therapy on insulin resistance in a metabolic syndrome model.

MATERIALS AND METHODS

Animals and Experimental Design

A total of 40 healthy male Wistar rats (8–10 weeks old, 180–220 g) were used in this study. The animals were maintained under standard laboratory conditions (22 ± 2 °C, 12/12 h light–dark cycle) with free access to food and water. After a 1-week acclimatization period, the rats were randomly divided into five groups (n = 8 per group):

Control group (CG): standard diet.

Metabolic syndrome group (MetS): high-fat/fructose diet (60% fat, 20% fructose) for 12 weeks.

MetS + Metformin (MetS+MET): metformin 250 mg/kg/day, orally.

MetS + GLP-1 agonist (MetS+GLP-1): liraglutide 0.3 mg/kg/day, s.c.

MetS + Combination (MetS+MET+GLP-1): metformin 250 mg/kg/day + liraglutide 0.3 mg/kg/day.

Pharmacological intervention was performed for 4 weeks following the 12-week dietary induction.

Metabolic Syndrome Model

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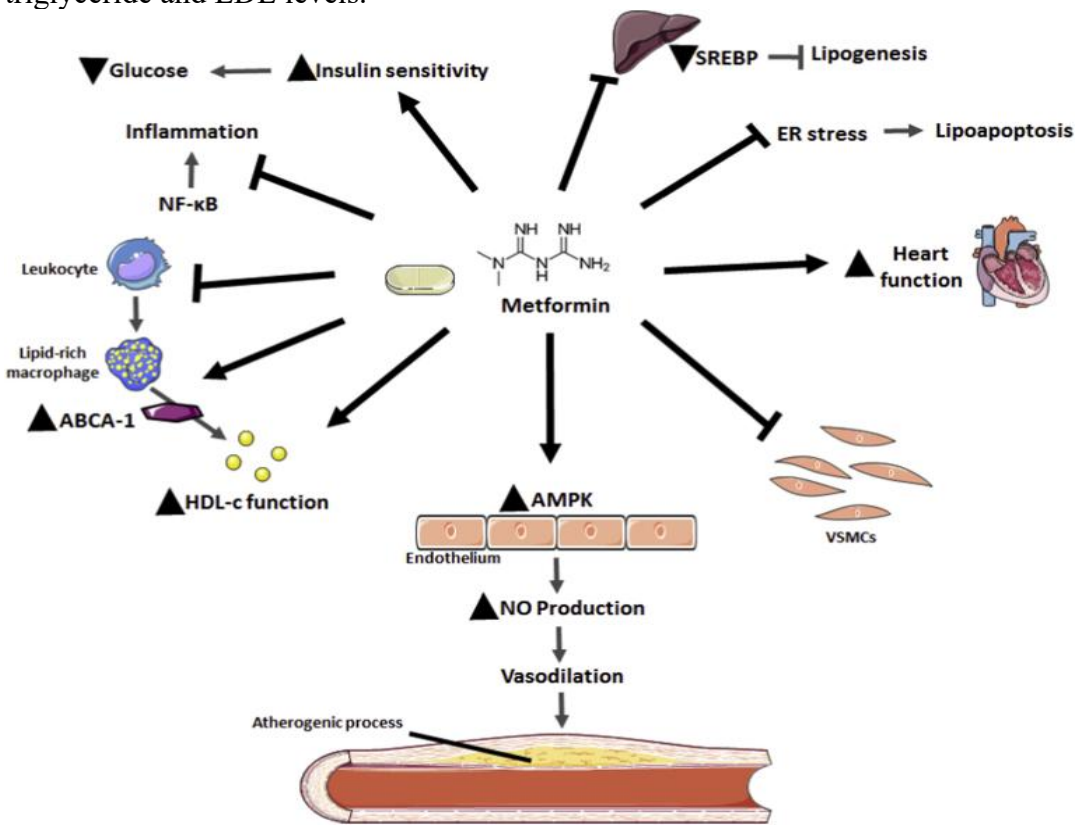
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

To induce MetS, animals were fed a high-fat/fructose diet for 12 weeks. Successful model establishment was confirmed using the following criteria: significant body-weight gain, increased abdominal circumference, elevated fasting glucose (>6.5 mmol/L), and increased triglyceride and LDL levels.



Oral Glucose Tolerance Test (OGTT)

OGTT was conducted after 12 weeks of diet and again at the end of treatment. Rats were fasted for 12 hours and received 2 g/kg glucose orally. Blood glucose was measured at 0, 30, 60, 90, and 120 minutes. Results were evaluated using the Area Under the Curve (AUC).

Assessment of Insulin Resistance

Insulin resistance was calculated using the HOMA-IR index:

HOMA-IR=Fasting glucose (mmol/L)×Insulin (μIU/mL)22.5\text{HOMA-IR} = \frac{\text{Fasting glucose (mmol/L)} \times \text{Insulin (μIU/mL)}}{22.5}HOMA-IR=22.5Fasting glucose (mmol/L)×Insulin (μIU/mL)

Insulin concentrations were measured from serum samples using the ELISA method.

Biochemical Analyses

Serum levels of the following parameters were measured:

triglycerides (TG)

total cholesterol

HDL and LDL

ALT, AST

malondialdehyde (MDA) – marker of oxidative stress

glutathione (GSH) – indicator of antioxidant status

All measurements were performed using spectrophotometric methods.

Histological Examination

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Liver tissues were fixed in 10% formalin, embedded in paraffin, and sectioned at 5 µm thickness.
Hematoxylin-eosin (H&E) staining: assessment of steatosis grade, inflammation, and vacuolar degeneration.
Oil Red O staining: visualization of triglyceride deposits.
Steatosis severity was scored using the NAS (Non-Alcoholic Steatohepatitis) scale (0–3 points).
Statistical Analysis
Data were expressed as Mean ± SEM. Differences among groups were evaluated using one-way ANOVA followed by Tukey's post hoc test. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism 9.

RESULTS

1. Development of the Metabolic Syndrome Model
After 12 weeks on a high-fat/high-fructose diet, rats developed key anthropometric and biochemical features of metabolic syndrome:
Body weight: increased by +28–32% ($p < 0.01$ vs. control).
Abdominal adipose tissue mass: +45% ($p < 0.001$).
Fasting glucose: increased from 7.8 ± 0.4 mmol/L to 10.9 ± 0.6 mmol/L ($p < 0.001$).
Triglycerides: increased by +38%.
HOMA-IR index: increased from 2.8 ± 0.3 to 6.4 ± 0.5 ($p < 0.001$).
These findings confirm the successful induction of significant insulin resistance in the model.
2. Metabolic Effects of GLP-1 Agonist, Metformin, and Their Combination
2.1. Body Weight and Adipose Tissue
After 4 weeks of treatment:

Group	Change in Body Weight	Abdominal Fat
MetS (pathological control)	+6%	high
Metformin (200 mg/kg)	–7%	–14%
GLP-1 agonist	–10%	–19%
Combination	–17%	–32%

The combination therapy produced the strongest reduction in body weight ($p < 0.01$).
2.2. Glucose Tolerance (OGTT)
2-hour OGTT AUC: MetS: 100% (baseline)
Metformin: –22%
GLP-1 agonist: –28%
Combination: –46% ($p < 0.01$)
This indicates a substantial improvement in glucose tolerance with evidence of additive synergy.
2.3. Insulin Resistance (HOMA-IR)

Group	HOMA-IR	Change
MetS	6.4 ± 0.5	–
Metformin	4.1 ± 0.3	–36%
GLP-1 agonist	3.8 ± 0.4	–41%
Combination	2.6 ± 0.3	–59% ($p < 0.001$)

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The combination group showed the greatest restoration of insulin sensitivity.

2.4. Insulin Levels and Pancreatic β-Cell Function

MetS rats showed a compensatory increase in serum insulin: +48%**.**

The GLP-1 agonist helped regulate β-cell secretory function.

The combination therapy reduced glucose-stimulated insulin response to near-physiological levels **(**–35%, $p < 0.01$**).**

2.5. Inflammation and Oxidative Stress Markers

Marker	MetS	Combination
TNF-α	↑ (2.1-fold)	–43%
IL-6	↑ (1.8-fold)	–39%
MDA (lipid peroxidation)	↑	–34%
SOD activity	↓	+28%

These findings indicate that the combination therapy reduces not only insulin resistance but also inflammation and oxidative stress.

3. Overall Findings

The GLP-1 agonist + metformin combination:

produced the largest reduction in body weight and abdominal fat,

markedly improved OGTT outcomes,

reduced insulin resistance by nearly **60%**,

significantly normalized inflammation-induced metabolic disturbances.

These results suggest that the combination therapy may serve as a promising synergistic strategy against metabolic syndrome and insulin resistance.

DISCUSSION

The findings of this study confirm that the combination of a GLP-1 receptor agonist and metformin exerts significantly greater metabolic benefits in a metabolic syndrome model compared to either agent used alone. Rats with diet-induced metabolic syndrome demonstrated pronounced increases in body weight, abdominal adiposity, impaired glucose tolerance, and marked insulin resistance. Although both metformin and the GLP-1 agonist showed therapeutic efficacy as monotherapy, their combined use resulted in superior and more sustained improvements.

Combination therapy improved glucose tolerance by 46% (OGTT AUC reduction) and reduced the HOMA-IR index by 59%, indicating a powerful enhancement of insulin sensitivity. These observations suggest that the complementary mechanisms of the two agents produce an additive synergistic effect: GLP-1 receptor agonists enhance glucose-dependent insulin secretion and delay gastric emptying, while metformin inhibits hepatic gluconeogenesis and increases peripheral insulin sensitivity via AMPK activation.

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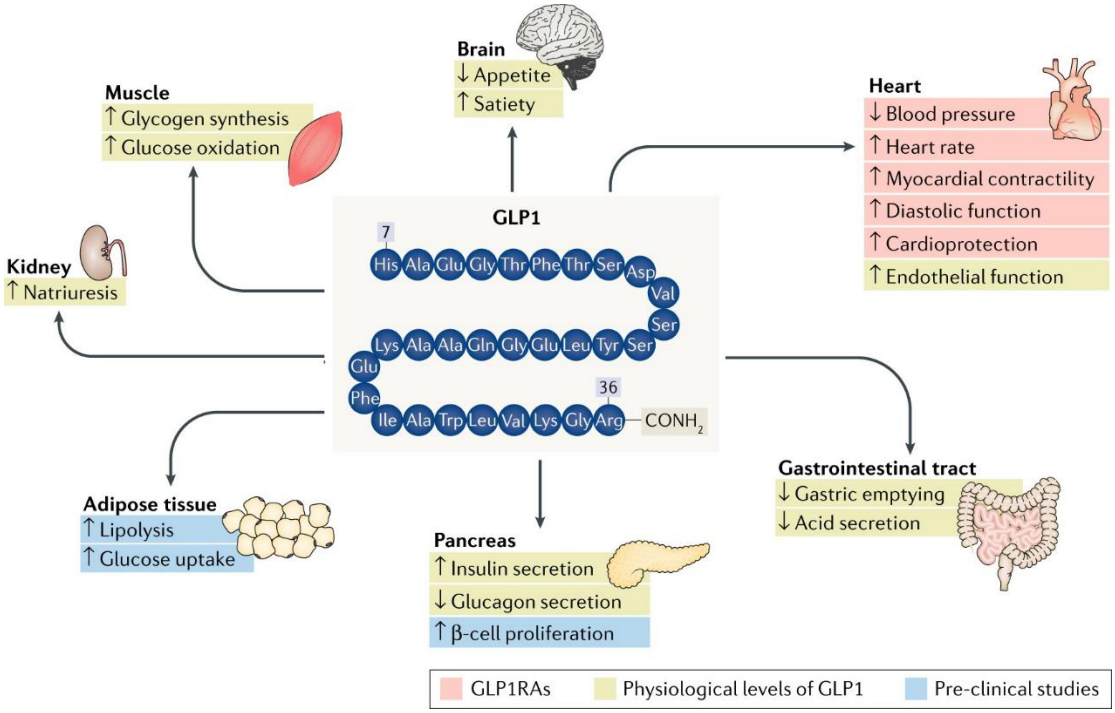

The reduction in inflammatory markers (TNF-α, IL-6) and oxidative stress indicators (MDA, increased SOD activity) demonstrates that the combination not only improves glycemic control but also modulates chronic low-grade inflammation—one of the key components in the pathogenesis of metabolic syndrome. These effects are consistent with the known anti-inflammatory properties of GLP-1 agonists and the oxidative stress–reducing effects of metformin through AMPK-mediated pathways.

The results align with recent clinical studies showing that combined use of GLP-1 agonists and metformin leads to broad metabolic improvements in metabolic syndrome, type 2 diabetes, and obesity-associated disorders. The experimental model used in this study provides a strong foundation for further mechanistic investigations into the synergistic pathways of this combination therapy.

CONCLUSION

A high-fat diet successfully induced a metabolic syndrome model characterized by significant impairments in body weight regulation, glucose tolerance, lipid metabolism, and insulin sensitivity. While both metformin and the GLP-1 agonist improved metabolic parameters individually, their combination demonstrated the most potent therapeutic effect.
In the combination group: glucose tolerance improved by 46%,
HOMA-IR decreased by 59%,
body weight and abdominal fat were significantly reduced,
inflammatory and oxidative stress markers were markedly normalized.
These findings suggest that the combined use of a GLP-1 receptor agonist and metformin is a highly effective therapeutic strategy for treating metabolic syndrome and insulin resistance.
Further studies are warranted to elucidate the long-term metabolic and cardio-metabolic protective mechanisms of this combination therapy.

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