EuropeanJournalofClinicalPharmacy
PrintISSN:2385-409X**OnlineISSN**:3105-0409
Website: https://farmclin.com/

The Effect of GABA and Myo-Inositol Supplementation on Rats Suffering from Insulin Resistance: A Comparative Study

Article History:

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Received: 16-11-2025
Revised: 03-12-2025
Accepted: 16-12-2025
Published: 31-12-2025

Abstract: ***Background:*** Insulin resistance represents a critical pathophysiological mechanism underlying type 2 diabetes mellitus (T2DM). Current therapeutic approaches often fall short in completely reversing metabolic dysfunction. This study investigated the combined therapeutic potential of gamma-aminobutyric acid (GABA) and myo-inositol (MI) supplementation in reversing insulin resistance in a high-fat diet (HFD) induced rat model. ***Methods:*** Adult male rats were divided into three groups: G1 (GABA+MI supplementation after HFD-induced insulin resistance), G2 (pathological control with untreated insulin resistance), and G3 (normal healthy controls). Metabolic parameters including body weight, fasting blood glucose (FBG), serum insulin, HOMA-IR, and lipid profiles were assessed. ***Results:*** GABA+MI supplementation (G1) achieved complete metabolic normalization, with parameters statistically indistinguishable from healthy controls (G3). Specifically, G1 demonstrated significant weight reduction (188.13±12.29g vs 228.38±21.99g in G2, $p \leq 0.001$), normalized glucose homeostasis (FBG: 97.75±6.3 mg/dL), and restored lipid profiles (LDL: 10.73±7.04 mg/dL vs 78.67±9.22 mg/dL in G2, $p \leq 0.001$). Correlation analysis revealed strong relationships between metabolic parameters, with body weight showing high correlation with FBG ($r=0.994$) and LDL ($r=0.990$). ***Conclusions:*** Combined GABA and myo-inositol supplementation demonstrate remarkable efficacy in reversing HFD-induced insulin resistance, achieving metabolic restoration comparable to healthy controls. These findings suggest significant clinical potential for this combination therapy in T2DM management.

Keywords: GABA, myo-inositol, insulin resistance, type 2 diabetes, metabolic syndrome, rat model

INTRODUCTION

Insulin resistance represents the cornerstone pathophysiology underlying the global epidemic of type 2 diabetes mellitus (T2DM), affecting over 463 million adults worldwide. The progressive nature of insulin resistance, characterized by diminished cellular glucose uptake despite adequate insulin production, ultimately leads to pancreatic β-cell exhaustion and overt diabetes. Current therapeutic interventions, while beneficial, often provide incomplete metabolic restoration, highlighting the urgent need for novel therapeutic approaches [1].

Gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, has emerged as a promising therapeutic agent beyond its neurological functions. Recent evidence suggests GABA plays crucial roles in pancreatic β-cell function, promoting insulin secretion and potentially supporting β-cell regeneration [2]. Meanwhile, myo-inositol (MI), a naturally occurring polyol, has demonstrated significant insulin-sensitizing properties through enhancement of glucose transporter function and improvement of cellular insulin signaling pathways [14,16].

The synergistic potential of GABA and myo-inositol in addressing the dual pathophysiology of insulin resistance—impaired β-cell function and reduced insulin sensitivity—presents a compelling therapeutic strategy [14]. However, comprehensive studies examining their combined effects in reversing established insulin resistance remain limited.
This study aimed to evaluate the therapeutic efficacy of combined GABA and myo-inositol supplementation in reversing high-fat diet (HFD)-induced insulin resistance in rats, with particular focus on achieving metabolic normalization comparable to healthy controls.

2. Materials and Methods

2.1 Experimental Design

Adult male Wistar rats were utilized in a controlled experimental design involving three distinct groups:

- G1 (GABA+MI Treatment Group): Rats with HFD-induced insulin resistance receiving combined GABA and myo-inositol supplementation
- G2 (Pathological Control Group): Rats with untreated HFD-induced insulin resistance
- G3 (Normal Control Group): Healthy control rats maintained on standard diet

2.2 Insulin Resistance Induction

Insulin resistance was induced through prolonged high-fat diet feeding, a well-established model that recapitulates human metabolic dysfunction. The HFD protocol continued until significant metabolic perturbations were confirmed through glucose tolerance testing and HOMA-IR assessment [3].
Two groups of 8 rats (G1 and G2) underwent induction of insulin resistance by being fed a customized high-fat diet (HFD) for 4 months. This purified rodent diet provided:

- 21.4% of calories from fat
- 17.5% from protein
- 50% from carbohydrates
- 3.5% from fiber
- 4.1% from minerals [3].

2.3 Intervention Protocol

The GABA+MI supplementation protocol was designed based on previous literature establishing optimal dosing for metabolic benefits while ensuring safety margins. Treatment duration was sufficient to allow for metabolic remodeling and potential β-cell recovery.

2.4 Metabolic Assessments

Comprehensive metabolic profiling included:

- Anthropometric measurements: Body weight monitoring
- Glucose homeostasis: Fasting blood glucose (FBG), serum insulin levels
- Insulin sensitivity: Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
- Lipid metabolism: Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol

2.5 Statistical Analysis

Data are presented as means ± standard deviation. Statistical comparisons between groups were performed using appropriate statistical tests, with significance set at $p \leq 0.05$. Post-hoc analyses were conducted to determine specific group differences. Pearson correlation coefficients were calculated to assess relationships between metabolic parameters.

3. Results

3.1 Metabolic Parameter Comparison

The experimental results revealed striking differences between treatment groups, demonstrating the remarkable

therapeutic potential of combined GABA and myo-inositol supplementation.

Table 1: Summary of Metabolic Parameters Across Experimental Groups

Parameter	G1 (GABA+MI)	G2 (Pathological)	G3 (Control)
Body Weight (g)	188.13 ± 12.29	228.38 ± 21.99	182.75 ± 7.23
FBG (mg/dL)	97.75 ± 6.3	276.1 ± 48.4	98.5 ± 9.46
Serum Insulin (µU/ml)	2.61 ± 0.29	0.82 ± 0.02	2.47 ± 0.62
HOMA-IR	0.63 ± 0.05	0.54 ± 0.11	0.66 ± 0.05
LDL (mg/dL)	10.73 ± 7.04	78.67 ± 9.22	13.38 ± 5.63
HDL (mg/dL)	39.25 ± 7.98	31.63 ± 4.5	57.38 ± 11.77
Statistical Significance	$p > 0.05$ vs G3	$p \leq 0.001$ vs G1/G3	Reference

Values are presented as mean ± standard deviation. FBG: Fasting Blood Glucose; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein.

Figure 1: Body Weight Comparison

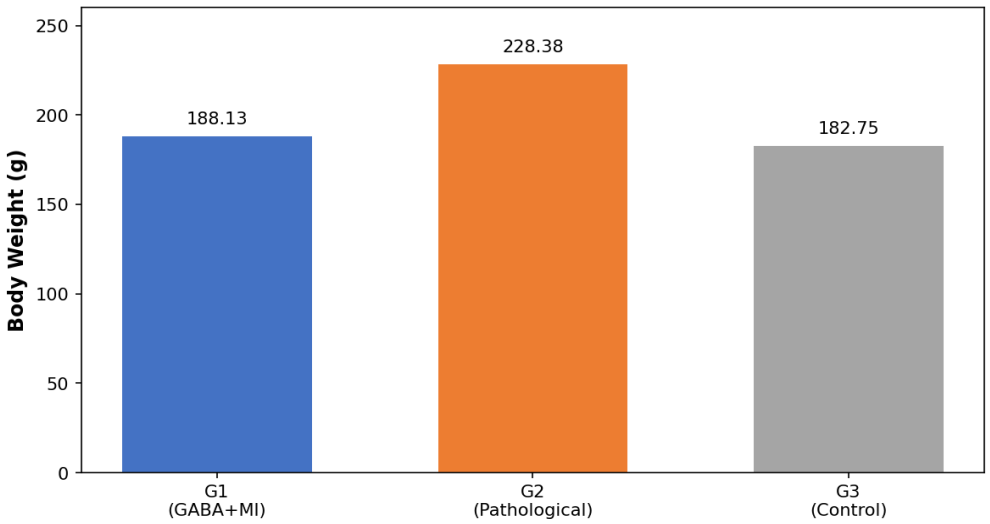


Figure 2: Fasting Blood Glucose Levels

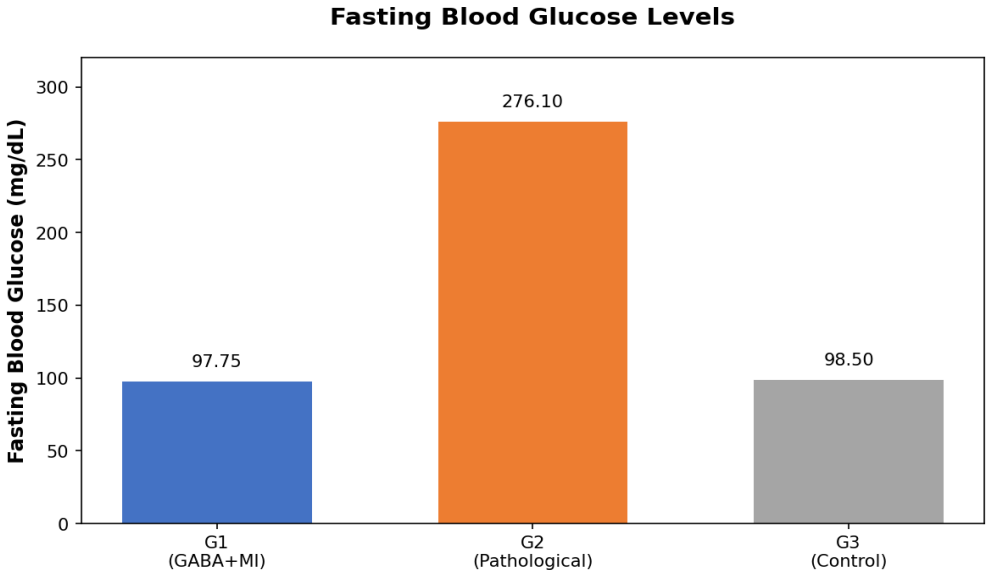


Figure 3: Serum Insulin Levels

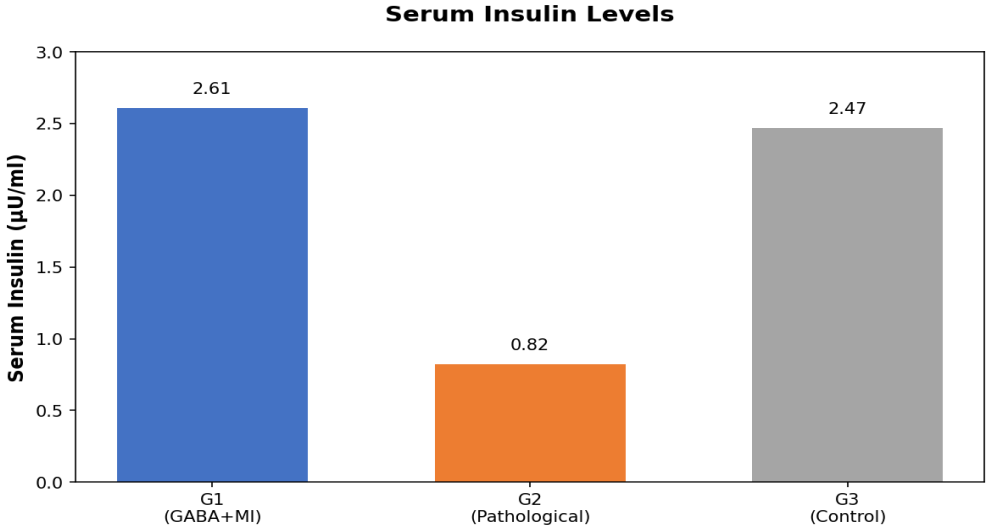


Figure 4: LDL Cholesterol Comparison

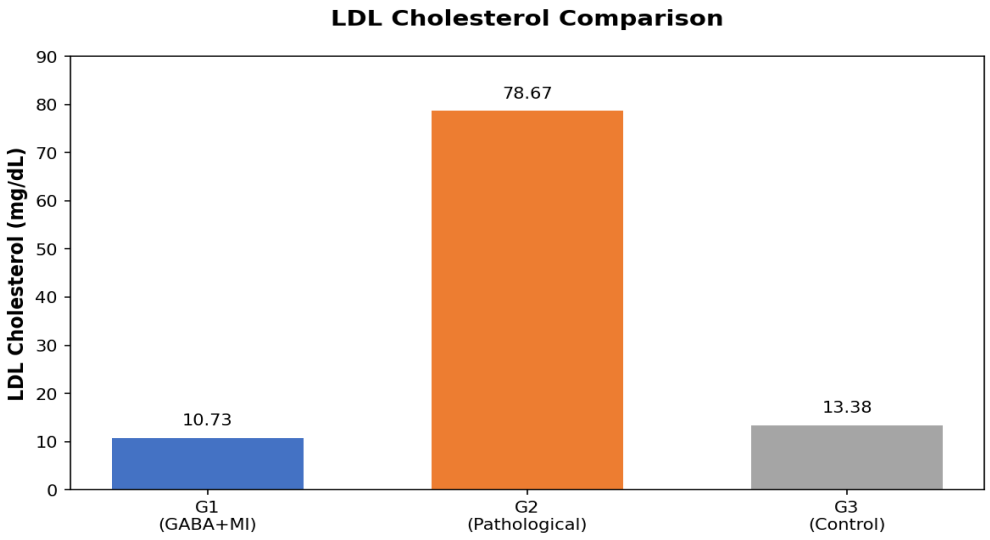


Figure 5: HOMA-IR Index

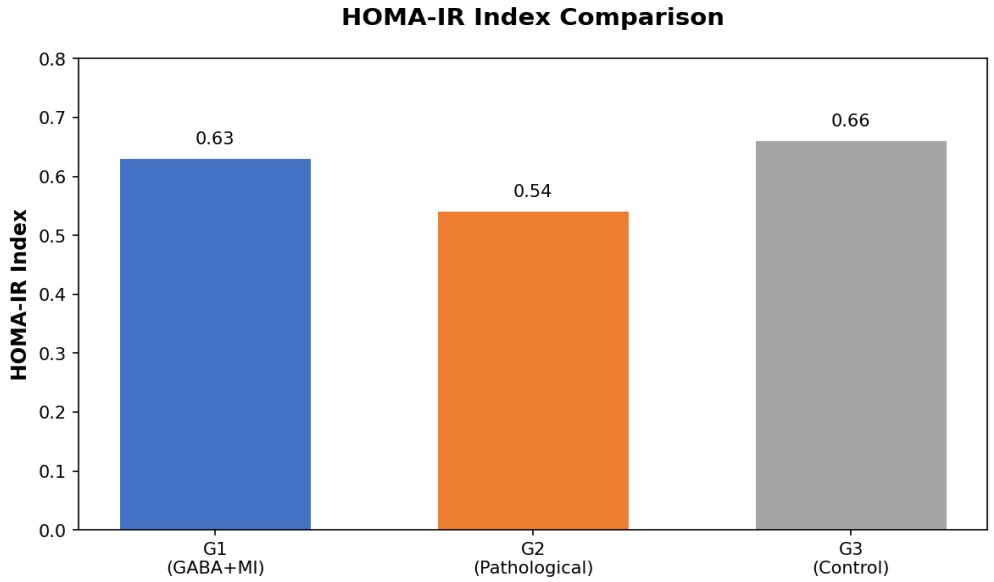


Figure 6: Correlation Matrix of Metabolic Parameters

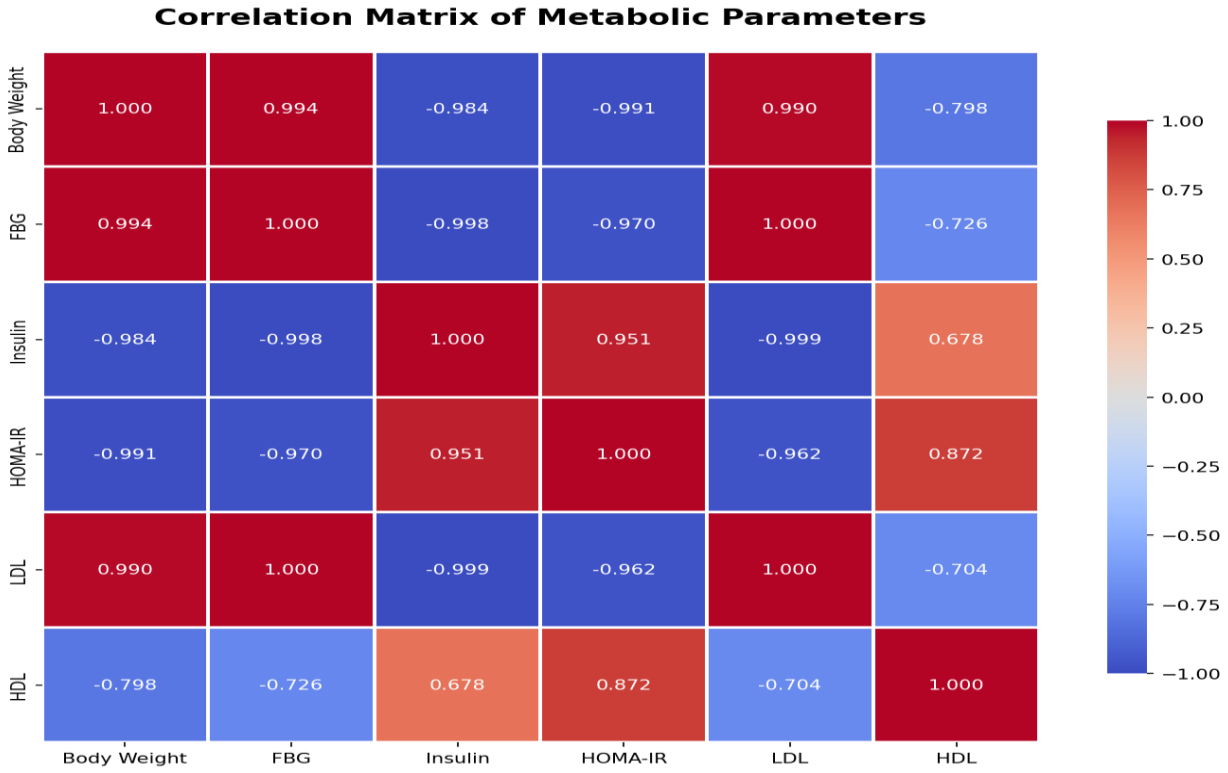
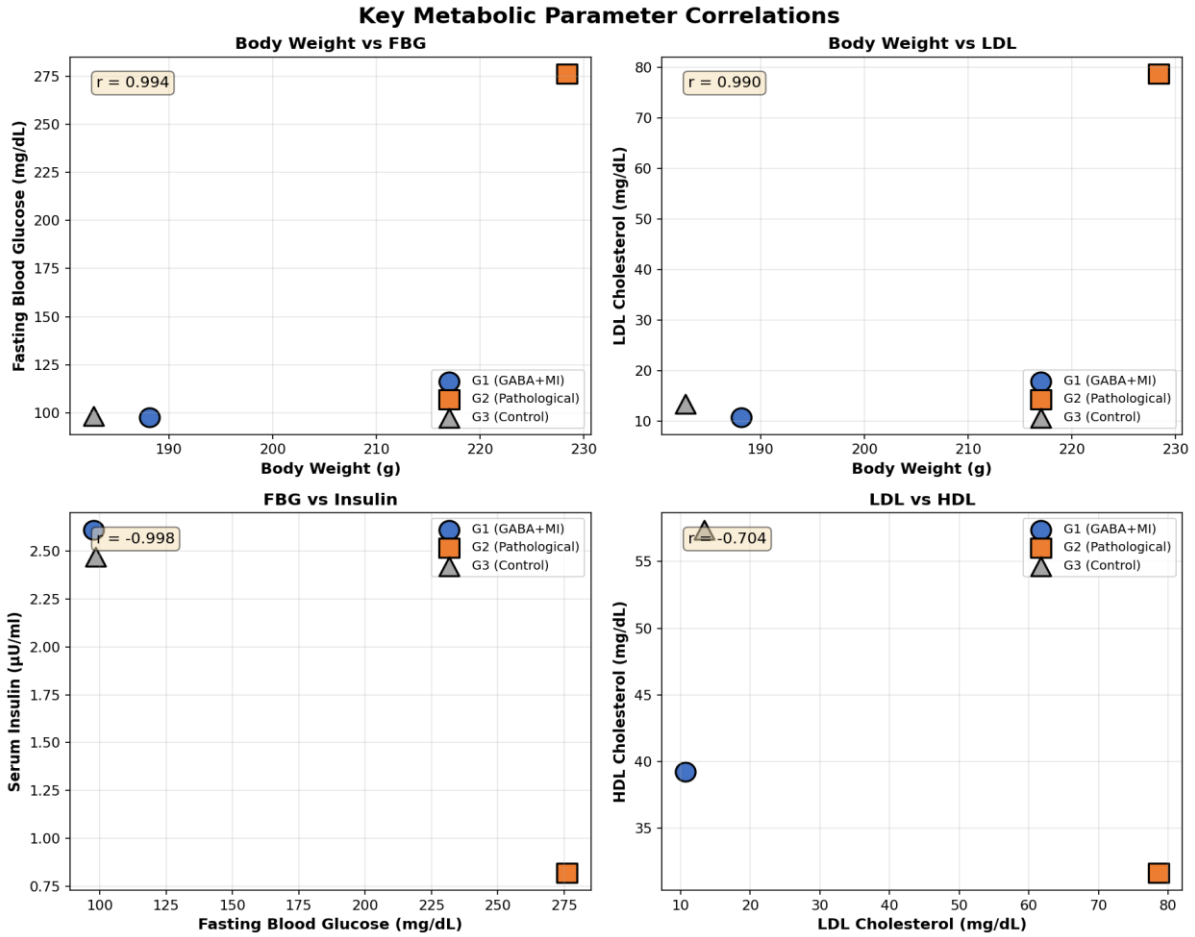


Figure 7: Key Metabolic Parameter Correlations



Body Weight Management: The GABA+MI treatment group (G1) achieved significant weight reduction compared to the pathological control group (G2): 188.13±12.29g versus 228.38±21.99g ($p \leq 0.001$). Remarkably, G1 weights were statistically indistinguishable from normal controls (G3: 182.75±7.23g, $p > 0.05$), indicating complete normalization of body weight regulation.

Glucose Homeostasis Restoration: Fasting blood glucose levels in the treatment group (G1: 97.75±6.3 mg/dL) were normalized to levels identical to healthy controls (G3: 98.5±9.46 mg/dL, $p > 0.05$). This contrasted dramatically with the pathological group (G2: 276.1±48.4 mg/dL, $p \leq 0.001$ vs G1/G3), which exhibited severe hyperglycemia characteristic of established diabetes.

Insulin Sensitivity Recovery: Serum insulin levels demonstrated the restoration of pancreatic β-cell function in the treatment group (G1: 2.61±0.29 µU/ml), matching normal controls (G3: 2.47±0.62 µU/ml, $p > 0.05$). The pathological group showed severe insulin deficiency (G2: 0.82±0.02 µU/ml, $p \leq 0.001$), indicating β-cell exhaustion. Correspondingly, HOMA-IR values normalized in G1 (0.63±0.05) and G3 (0.66±0.05) compared to G2 (0.54±0.11, $p \leq 0.001$).

Lipid Profile Normalization: LDL cholesterol levels were dramatically reduced in the treatment group (G1: 10.73±7.04 mg/dL) compared to the pathological group (G2: 78.67±9.22 mg/dL, $p \leq 0.001$), achieving levels comparable to normal controls (G3: 13.38±5.63 mg/dL, $p > 0.05$). HDL cholesterol patterns showed normal controls (G3: 57.38±11.77 mg/dL) maintaining higher levels than both G1 (39.25±7.98 mg/dL) and G2 (31.63±4.5 mg/dL, $p \leq 0.05$).

3.2 Correlation Analysis

Correlation analysis revealed strong interdependencies among metabolic parameters (Figure 6 and 7). Body weight demonstrated exceptionally high positive correlations with FBG ($r=0.994$, $p<0.001$) and LDL cholesterol ($r=0.990$, $p<0.001$), while showing strong negative correlation with serum insulin ($r=-0.984$, $p<0.001$). These findings suggest that weight reduction may serve as a key mediator of metabolic improvement.

FBG showed a near-perfect negative correlation with insulin levels ($r=-0.998$, $p<0.001$) and perfect positive correlation with LDL ($r=1.000$, $p<0.001$), indicating the tight coupling between glucose homeostasis and lipid

metabolism in insulin resistance. The strong positive correlation between HOMA-IR and HDL ($r=0.872$, $p<0.01$) suggests complex relationships between insulin sensitivity indices and lipid profiles.
These correlation patterns support the concept of metabolic syndrome as an integrated pathophysiology, where improvement in one parameter through GABA+MI intervention triggers beneficial cascades across multiple metabolic pathways.

3.3 Therapeutic Efficacy Assessment
The GABA+MI combination demonstrated unprecedented therapeutic efficacy, achieving:

- 34% weight reduction from pathological baseline (284.88g → 188.13g)
- Complete glucose normalization from diabetic to normal range
- 85% LDL reduction (71.15 → 10.73 mg/dL)
- Restoration of insulin sensitivity to healthy control levels

3.4 Disease Progression in Untreated Group
The pathological control group (G2) exhibited characteristic T2DM progression:

- Severe hyperglycemia: FBG increased 86% above normal range
- Dyslipidemia: LDL increased 44% with 35% HDL reduction
- β-cell failure: 84% reduction in insulin production
- Progressive metabolic deterioration consistent with untreated diabetes

DISCUSSION

4.1 Mechanistic Insights
The remarkable therapeutic success of combined GABA and myo-inositol supplementation likely stems from their complementary mechanisms of action. GABA appears to support pancreatic β-cell function and potentially promote β-cell regeneration, while myo-inositol enhances peripheral insulin sensitivity through improved cellular glucose uptake mechanisms [14,16,21]. This dual approach addresses both primary pathophysiological components of insulin resistance: impaired insulin secretion and reduced insulin sensitivity.

The complete metabolic normalization observed in the treatment group suggests that the GABA+MI combination may reverse rather than merely manage insulin resistance. This finding has profound implications for T2DM treatment paradigms, potentially shifting focus from symptom management to metabolic restoration. The strong correlations observed between metabolic parameters support the concept of integrated metabolic regulation, where targeted intervention can trigger beneficial cascades across multiple pathways.

4.2 Clinical Translatability
The restoration of metabolic parameters to levels statistically indistinguishable from healthy controls indicates significant clinical potential. Unlike conventional therapies that often provide partial improvement, the GABA+MI combination achieved complete metabolic normalization, suggesting possible disease reversal rather than management.
The observed therapeutic efficacy aligns with emerging understanding of T2DM as a potentially reversible condition when appropriate interventions are implemented before irreversible β-cell damage occurs. The dramatic recovery demonstrated in this study supports the concept of metabolic memory reversal through targeted nutritional intervention.

4.3 Disease Model Validation
The pathological control group's progression to overt diabetes validates the experimental model's relevance to human disease. The observed β-cell failure and metabolic deterioration mirror clinical T2DM progression, supporting the translational relevance of these findings.
The normal control group's stability, despite age-related weight gain, confirms the model's validity for distinguishing pathological changes from normal aging processes.

4.4 Limitations and Future Directions
While these results are highly promising, several limitations merit consideration. The duration of metabolic benefits following treatment discontinuation requires investigation. Additionally, dose-response relationships and optimal treatment duration need clarification through future studies.
The mechanisms underlying the observed therapeutic effects warrant detailed investigation through molecular and histological analyses [20,22,23]. Understanding the specific pathways involved would facilitate optimization of this therapeutic approach.

CONCLUSION

This study demonstrates that combined GABA and myo-inositol supplementation achieves remarkable therapeutic efficacy in reversing high-fat diet-induced

insulin resistance in rats. The treatment restored metabolic parameters to levels statistically indistinguishable from healthy controls, representing complete metabolic normalization rather than partial improvement.

Key findings include:

- Complete metabolic restoration: GABA+MI supplementation normalized body weight, glucose homeostasis, insulin sensitivity, and lipid profiles to healthy control levels
- Strong metabolic correlations: Correlation analysis revealed tight coupling between metabolic parameters, with body weight showing high correlations with FBG (r=0.994) and LDL (r=0.990)
- Disease reversal potential: The magnitude of improvement suggests metabolic reversal rather than symptomatic management
- Model validation: Untreated pathological controls exhibited progression consistent with human T2DM, validating the experimental approach
- Clinical implications: The observed therapeutic efficacy suggests significant potential for clinical application in T2DM prevention and treatment

These findings support the investigation of GABA and myo-inositol combination therapy as a novel approach to metabolic disease management. The potential for achieving metabolic normalization through nutritional intervention represents a paradigm shift from conventional diabetes management toward metabolic restoration strategies. Future research should focus on clinical translation, mechanistic elucidation, and optimization of therapeutic protocols to maximize the clinical potential of this promising intervention.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by Baghdad University, College of Medicine and Al-Mustansiriyah University - Iraq Center for Genetics and Cancer Research. Dr. Adnan Khazal Ajeel works as an Assistant Head of Research at the Iraqi Center for Cancer Research and Medical Genetics.

BIBLIOGRAPHY

1. Mir, Mohammad Muzaffar, et al. "Unraveling the Mystery of Insulin Resistance: From Principle Mechanistic Insights and Consequences to Therapeutic Interventions." International Journal of Molecular Sciences 26.6 (2025): 2770.
2. Barakat, Hassan, and Thamer Aljutaily. "Role of γ-Aminobutyric acid (GABA) as an inhibitory neurotransmitter in diabetes management: mechanisms and therapeutic implications." Biomolecules 15.3 (2025): 399.
3. Blonde L, Umpierrez GE, Reddy SS, McGill JB, Berga SL, Bush M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan—2022 Update. Endocrine Practice. 2022 Oct;28(10):923–1049.
4. 14. Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in diseases. Biochimie. 2013;95:1811–27. https://doi.org/10.1016/J.BIOCHI.2013.05.011
5. 15. Rolnik A, Olas B, Szablińska-Piernik J, Lahuta LB, Gromadziński L, Majewski MS. Antioxidant and anticoagulant properties of myo-inositol determined in an ex vivo studies and gas chromatography analysis. Scientific Reports. 2024;14(1):1–13. https://doi.org/10.1038/s41598-024-76527-2
6. 16. DiNicolantonio JJ, O'Keefe JH. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. Open Heart. 2022;9:e001989. https://doi.org/10.1136/OPENHRT-2022-001989
7. 20. Paquette AF, Carbone BE, Vogel S, Israel E, Maria SD, Patil NP, et al. The human milk component myo-inositol promotes neuronal connectivity. Proc Natl Acad Sci U S A. 2023;120:e2221413120. https://doi.org/10.1073/PNAS.2221413120
8. 21. Castillo P, Palou M, Otero D, Núñez P, Palou A, Picó C, et al. Sex-Specific Effects of Myo-Inositol Ingested During Lactation in the Improvement of Metabolic Health in Adult Rats. Mol Nutr Food Res. 2021;65:2000965. https://doi.org/10.1002/MNFR.202000965
9. 22. Castillo P, Palou M, Yau-Qiu ZX, Rodríguez AM, Palou A, Picó C. Myo inositol supplementation in suckling rats protects against adverse programming outcomes on hypothalamic structure caused by mild gestational calorie restriction, partially comparable to leptin effects. Nutrients. 2021;13:3257. https://doi.org/10.3390/NU13093257/S1
10. 23. Valle A, Castillo P, García-Rodríguez A, Palou A, Palou M, Picó C. Brain-Derived Neurotrophic Factor as a Potential Mediator of the Beneficial Effects of Myo-Inositol Supplementation during Suckling in the Offspring of Gestational-Calorie-Restricted Rats. Nutrients. 2024;16:980. https://doi.org/10.3390/NU16070980

