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Antidiabetic Effects of Gymnema sylvestre and Metformin Co-Therapy in a Type 2 Diabetic Rat Model

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Research Article

Keywords: Gymnema sylvestre, Metformin, Streptozotocin, Type 2 Diabetes Mellitus, Insulin Sensitivity, Combination Therapy

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and hyperglycemia. Metformin is the standard therapy, however plant-based adjuncts such as *Gymnema sylvestre* (GS) are gaining interest for their anti-diabetic potential.

Objectives: To evaluate the anti-diabetic effects of GS, alone and with metformin, on glycemic control, lipid profile, renal function, and body weight in high-fat diet and streptozotocin (STZ)-induced T2DM rats.

Methods: Thirty male Sprague Dawley rats (150 ± 20 g) were divided into five groups: normal control, diabetic control (DC), metformin-treated (Met), GS-treated, and combination-treated (Met + GS). T2DM was induced by 21 days of high-fat diet followed by two STZ injections (25 mg/kg, five days apart). Rats with fasting blood glucose (FBG) ≥270 mg/dL were treated for 28 days. Biochemical parameters (FBG, HbA1c, serum creatinine, and cholesterol) and body weight were assessed.

Results: By Day 28, all treatment groups showed significant improvements compared to DC ($p < 0.05$). Metformin produced the greatest reductions in FBG, cholesterol, creatinine, and HbA1c. GS monotherapy had modest but significant effects, while Met + GS improved glycemic control and lipid profile more effectively than GS alone. Metformin remained superior in renal protection. All treated groups showed significantly higher body weights than DC, indicating protection against STZ-induced weight loss.

Conclusion: This study demonstrated that Metformin and GS, individually and in combination, improved glycemic control and metabolic outcomes in T2DM rats. While metformin showed the greater efficacy, combination therapy provided additive benefits, supporting GS as a potential adjunct in T2DM management.

Keywords: *Gymnema sylvestre,* Metformin, Streptozotocin, Type 2 Diabetes Mellitus, Insulin Sensitivity, Combination Therapy.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. It poses a major global health burden due to its increasing prevalence and associated complications such as cardiovascular disease, neuropathy, and nephropathy [1].

DM is primarily classified into two types: Type 1 and Type 2. Type 1 diabetes is an autoimmune condition marked by the destruction of pancreatic β-cells, leading to absolute insulin deficiency. Insulin therapy remains the cornerstone for its management to maintain glycemic control and prevent complications. Type 2 diabetes mellitus (T2DM), the more prevalent form, is characterized by insulin resistance and relative insulin deficiency [2].

Metformin, a biguanide compound, is the first-line oral antidiabetic drug for T2DM. It exerts its effects by reducing hepatic glucose production, enhancing peripheral glucose uptake, and improving insulin sensitivity [3]. While effective in glycemic control and in reducing the risk of diabetic complications, long-term metformin use may lead to adverse effects such as gastrointestinal disturbances and, rarely, lactic acidosis [4]. These limitations highlight the need for complementary or alternative therapies that are effective and safer.

In this context, *Gymnema sylvestre* (GS)-commonly known as "Gurmar" in Hindi, a woody climber from the Asclepiadaceae (milkweed) family, has garnered attention for its antidiabetic potential. Used for over 2000 years in Ayurvedic medicine, GS contains a range of bioactive phyto-constituents such as gymnemic acids, saponins, flavonoids, triterpenoids, and gurmarin—a polypeptide with hypoglycemic properties [5,6]. Among these, gymnemic acids are oleanane-type triterpenoid saponins that competitively inhibit glucose absorption in the intestines by occupying

glucose receptor sites on the gut mucosa [6]. Furthermore, they promote insulin secretion and enhance peripheral glucose utilization. The flavonoids and saponins also exhibit potent antioxidant activity, reducing oxidative stress and improving insulin sensitivity [6,7]. These multifaceted mechanisms support the plant's hypoglycemic, insulinotropic, and antioxidative effects, making it a promising adjunct in the management of T2DM [7].

Experimental models are crucial for studying the pathophysiology of T2DM and evaluating potential therapeutic agents. Streptozotocin (STZ), a nitrosourea derivative, is widely used in experimental diabetes due to its selective cytotoxicity towards pancreatic β-cells, resulting in sustained hyperglycemia [8]. However, to better replicate the complexity of human T2DM, a combination model involving a high-fat diet (HFD) followed by low-dose STZ is often used. The HFD induces insulin resistance through lipid metabolism disruption and impairment of insulin signaling, while STZ partially damages β-cells, mimicking their gradual decline [9]. This HFD/STZ model is widely accepted for its physiological relevance and reproducibility in preclinical diabetes research.

While both metformin and GS have independently demonstrated significant antidiabetic effects, few studies have investigated their combined therapeutic potential. Whether this combination produces additive or synergistic benefits remains uncertain, highlighting a critical gap in current diabetes research. Evaluating the co-administration of metformin and GS in an HFD/STZ-induced T2DM rat model may offer valuable insights into integrated therapeutic strategies for better diabetes management.

Accordingly, the present study aimed to assess the efficacy of GS in combination with metformin in reducing fasting blood glucose levels and body weight in STZ-induced diabetic rats. It further compared the therapeutic outcomes of the combination therapy with metformin monotherapy in achieving glycemic control and weight reduction. Additionally, the study evaluated the effects of the combination treatment

on lipid profile and renal function to provide a comprehensive understanding of its potential role in managing type 2 diabetes mellitus.

Materials and Methods

Study Design: Experimental Study

Sample Size Calculation: In this study, the sample size was determined using the resource equation method [10]. According to this method, “E” represents the degrees of freedom for analysis of variance (ANOVA), and its value should lie between 10 and 20.

The formula is: E=Total number of animals−Total number of groups

$$E = (N \times n) - N$$

Where: N = number of groups, n = number of animals per group. For this study: Number of groups (N) = 5, Animals per group (n) = 6. $E = (5 \times 6) - 5 = 30 - 5 = 25$

Since the calculated value of E exceeded the recommended range (10–20), corrections were applied considering biological factors. The efficacy of STZ in inducing T2DM is approximately 80% [11], and with an anticipated attrition rate of 20%, the effective sample size was adjusted to six animals per group. Thus, a total of 30 rats (six per group across five groups) were included in the study to ensure adequate statistical power and account for potential variability [12].

Drugs, Chemicals, and Supplements

- Streptozotocin (STZ): Obtained from Sisco Research Laboratories Pvt. Ltd. (Mumbai, India) in 500 mg vials.
- Preparation of Plant Extract: Hydroalcoholic extract of *Gymnema sylvestre* sourced from Arjuna Natural Pvt. Ltd. in Kerala, India.
- Metformin: Administered as OKAMET 500 mg tablets (Cipla Ltd., Haridwar, India).
- High-Fat Diet (HFD): The HFD consisted of 60% kcal from fat (primarily lard), 20% protein (casein), and 20% carbohydrates

(sucrose and corn-starch), sourced from Karyome Pvt. Ltd. (Mysuru, India)

- Other Reagents: Citric acid, sodium citrate, and sodium carboxymethyl cellulose (Na-CMC) were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used to prepare the citrate buffer.

Experimental Animals

Thirty male Sprague Dawley rats (6–8 weeks old, 150 ± 20 g) were obtained from the Central Animal Facility, MAMC. Rats were housed three per cage under standard laboratory conditions (25 ± 5 °C temperature, 55 ± 10% humidity, 12-hour light/dark cycle). All animals had ad libitum access to food and water. A one-week acclimatization period was allowed before initiating experiments. Animals were randomly allocated into five groups using computer-generated randomization.

Experimental Design

Phase 1: Induction of Type 2 Diabetes Mellitus (T2DM)

The HFD/STZ rat model for T2DM induction was based on a high-fat diet and low-dose STZ injections. Rats were fed a high-fat diet (HFD) ad libitum (approximately 20 g/rat/day), containing 60% fat, 20% protein, and 20% carbohydrates for 21 days to induce insulin resistance. Body weight was monitored weekly during this period. After 21 days, rats were given two intra-peritoneal injections of STZ (25 mg/kg body weight) prepared fresh in cold 0.1 mM citrate buffer (pH 4.5) to preserve STZ stability and enhance beta-cell toxicity with a 5-day break between injections. Fasting blood glucose (FBG) was measured three days after the second injection using a tail vein blood sample and glucometer. Rats with FBG ≥270 mg/dL were considered diabetic and enrolled for treatment.[7]

Phase 2: Drug Administration

Diabetic rats were randomly assigned to four groups (n = 6 per group), while non-diabetic rats were assigned to the normal control group:

- Group 1 (Normal Control): Normal rats received normal saline (10 mL/kg) via oral gavage for 4 weeks.
- Group 2 (Diabetic Control): Diabetic rats received normal saline (10 mL/kg) for 4 weeks.
- Group 3 (Metformin): Diabetic rats received metformin (200 mg/kg/day) via oral gavage for 4 weeks.
- Group 4 (GS): Diabetic rats received GS (600 mg/kg/day) via oral gavage for 4 weeks.
- Group 5 (Metformin + GS): Diabetic rats received both metformin (200 mg/kg/day) and GS (600 mg/kg/day) via oral gavage for 4 weeks.

Dosages were calculated based on previously published studies and the human equivalent dose (HED) conversion method.[9,10] Specifically, the dose of GS (600 mg/kg) was selected based on Mall et al. (2009), which demonstrated significant antidiabetic activity in alloxan-induced diabetic rats.

Blood Collection and Biochemical Parameters

Blood samples were collected via the retro-orbital plexus under ketamine (80 mg/kg) and xylazine (08 mg/kg) anesthesia. Approximately 0.4–0.5 mL of blood was collected into microcentrifuge tubes on Days 0, 7, and 28 for FBG analysis, and on Days 0 and 28 for HbA1c, serum creatinine, and total cholesterol. Samples were centrifuged at 4000 rpm for 15 minutes at 4°C, and plasma was stored at –80°C until analysis using a Semi-Automated Biochemistry Analyzer. Fasting Insulin levels were determined using a commercially available rat insulin ELISA kit (Invitrogen, Catalog No.: ERINS, Thermo Fisher India) as per the manufacturer’s protocol.

Statistical Analysis

All values were expressed as mean ± standard deviation (SD). Data were analyzed using two-way analysis of variance (ANOVA) followed by

Tukey’s post hoc test to assess differences between multiple treatment groups across time points. This method was chosen due to its robustness in detecting group differences in repeated measures and factorial designs. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 (Chicago, IL, USA).

Results

Diabetes Induction and Baseline Parameters: At baseline, no significant differences were observed in body weight or fasting blood glucose (FBG) levels among the experimental groups ($p > 0.05$). Following 21 days of high-fat diet (HFD) feeding and subsequent streptozotocin (STZ) administration, all diabetic groups exhibited significantly elevated FBG levels compared to the normal control (NC) group ($p < 0.05$), confirming successful induction of type 2 diabetes mellitus (T2DM) (Table-1).

Effects of Treatment on Biochemical and Physiological Parameters: After 28 days of treatment, all intervention groups—metformin (Met), GS, and their combination (Met + GS)—showed significant improvements in key biochemical and physiological parameters compared to the diabetic control (DC) group ($p < 0.05$). Among them, metformin produced the most pronounced improvements across all parameters. GS monotherapy resulted in moderate but significant effects, while the Met + GS combination demonstrated greater efficacy than GS alone but remained slightly less effective than metformin in most outcomes.

By Day 28, body weights in all treatment groups were significantly higher compared to the DC group ($p < 0.001$), indicating a protective effect against STZ-induced weight loss. The NC group, maintained on a standard pellet diet, exhibited significantly lower body weight than the HFD/STZ groups.

Fasting Blood Glucose (FBG): FBG levels were significantly reduced in the Met and Met + GS groups as early as Day 7 compared to DC ($p < 0.001$). On Day 7, reductions were significant in Met ($p = 0.030$) and Met + GS ($p = 0.004$) versus DC. By Day 28, all treatment groups exhibited significantly lower FBG levels compared to DC ($p < 0.001$). Pairwise comparisons indicated that Met + GS achieved superior glycemic control over GS ($p < 0.05$), although metformin remained more effective ($p = 0.01$ vs. Met + GS and GS). GS monotherapy produced only a modest reduction by Day 28, with no significant effect at Day 7 (Table 2; Fig. 2).

Total Serum Cholesterol: On Day 28, all treatment groups showed significantly reduced cholesterol levels compared to DC ($p < 0.001$). Two-way RM ANOVA confirmed that Met, GS, and Met + GS groups had substantially lower levels than DC. Pairwise comparisons revealed significant differences between Met and Met + GS ($p = 0.01$) and between Met and GS ($p < 0.05$) (Table 2; Fig. 3).

Blood Creatinine: On Day 28, all treatment groups demonstrated significantly reduced creatinine levels compared to DC ($p < 0.001$). Two-way RM ANOVA confirmed lower values in Met, GS, and Met + GS groups versus DC. Pairwise analysis showed significant differences between Met and Met + GS ($p = 0.01$) and between Met and GS ($p < 0.05$) (Table 2; Fig. 4).

HbA1c: On Day 28, HbA1c levels were significantly lower in all treatment groups compared to DC ($p < 0.001$). Two-way RM ANOVA confirmed substantial reductions in Met, GS, and Met + GS groups relative to DC. Pairwise comparisons revealed significant differences between Met and Met + GS ($p = 0.01$) and between Met and GS ($p < 0.05$) (Table 2; Fig. 5).

Discussion

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by chronic hyperglycemia, insulin resistance, and impaired insulin secretion. Its global prevalence is rising rapidly, contributing to

significant health and economic burdens worldwide. Although standard treatments like metformin remain the mainstay of therapy due to their proven efficacy and safety profile, there is increasing interest in adjunctive therapies, especially those derived from traditional medicinal plants, to enhance therapeutic outcomes and minimize side effects [13].

In the present study, T2DM was successfully induced in rats using a combination of a high-fat diet (HFD) followed by low-dose streptozotocin (STZ), effectively mimicking the dual pathophysiological mechanisms of insulin resistance and pancreatic β-cell dysfunction seen in human T2DM [14]. This model is widely recognized for evaluating the efficacy of antidiabetic agents due to its translational relevance and reproducibility.

Metformin, used as the standard comparator, significantly improved glycemic control and metabolic markers, including fasting blood glucose (FBG), serum cholesterol, creatinine, and glycated hemoglobin (HbA1c). These findings are consistent with extensive literature highlighting metformin’s ability to suppress hepatic gluconeogenesis, enhance insulin sensitivity, and improve lipid and renal profiles [15]. The observed nephroprotective effect may be attributed to metformin’s activation of AMP-activated protein kinase (AMPK), a mechanism known to protect against diabetic nephropathy and oxidative stress-related tissue damage [15].

Gymnema sylvestre (GS), a traditional Ayurvedic herb, demonstrated moderate anti-diabetic activity. Its bioactive constituents, particularly gymnemic acids, are known to reduce intestinal glucose absorption, stimulate insulin secretion, and protect pancreatic β-cells from oxidative damage [16, 17]. The modest improvements observed in the GS-treated group support its traditional use and pharmacological potential as a glucose-lowering agent. The improved reductions in cholesterol and creatinine imply beneficial effects on lipid homeostasis and kidney function. These findings are clinically relevant given the complexities of diabetic dyslipidemia and nephropathy.

Combination therapy with GS and metformin resulted in better outcomes than GS monotherapy across all measured parameters, suggesting additive effects. However, it did not significantly surpass metformin alone in most biochemical markers. This indicates that while GS may complement metformin through additional mechanisms, the interaction is likely additive rather than synergistic [14, 18]. Such herbal-drug combinations have been reported to provide multi-targeted benefits by modulating glycemic control, lipid metabolism, oxidative stress, and β-cell protection [19].

Notably, the combination therapy also improved cholesterol and creatinine levels, suggesting potential lipid-lowering and renoprotective benefits. This is of clinical importance given the high prevalence of dyslipidemia and nephropathy among diabetic patients [15, 20]. These effects may be due to the antioxidant and anti-inflammatory properties of GS compounds acting in concert with metformin’s metabolic regulation.

Despite these promising findings, the relatively lower efficacy of GS alone emphasizes the necessity of standard pharmacotherapy, particularly in cases of moderate to severe hyperglycemia. However, its role as an adjunct—especially in patients preferring integrative medicine or those intolerant to higher doses of metformin—warrants further exploration [21].

Limitations and Future Directions

This study offers preliminary evidence supporting the antidiabetic potential of *G. sylvestre* in combination with metformin, yet several limitations must be addressed. The short study duration (28 days) limits the ability to assess long-term metabolic effects, disease progression, or chronic safety profiles. Additionally, the small sample size (n = 6 per group) may reduce statistical power and increase the margin of error in detecting subtle intergroup differences.

Moreover, the study lacked advanced metabolic assessments such as oral glucose tolerance tests (OGTT) or insulin tolerance tests (ITT), which would have provided deeper insights into glucose homeostasis and insulin sensitivity. Another key limitation was the absence of histopathological evaluation of vital organs such as the pancreas, kidneys, and liver. Biochemical improvements alone cannot fully reflect the extent of tissue-level damage or repair, and the inclusion of histological analysis in future studies would greatly enhance mechanistic understanding.

Furthermore, the phytochemical profile of the GS extract used in this study was not characterized. Without detailed profiling and quantification of gymnemic acids or other active compounds, it is difficult to establish dose-effect relationships or identify the most potent constituents. Future research should focus on standardizing extract composition, extending treatment durations, increasing sample sizes, and incorporating comprehensive biochemical, histological, and molecular endpoints.

Conclusion

This study demonstrated that both metformin and GS, alone and in combination, exert significant anti-diabetic effects in STZ-induced T2DM rats. Metformin exhibited superior efficacy in lowering FBG, HbA1c, serum cholesterol, and creatinine levels. GS provided modest yet significant benefits, and its combination with metformin yielded additive improvements. These findings support the potential utility of GS as an adjunct therapy, though further research is necessary to validate its clinical applicability and long-term safety.

Data Availability Statement

The authors confirm that all data generated or analysed during this study are included in this published article. Additional datasets supporting the

conclusions of this article are available from the corresponding author upon reasonable request.

Author Contributions

Akhilesh Mishra was responsible for the conceptualization, hypothesis of the study, data collection, analysis, and manuscript drafting. Vandana Roy provided supervision and contributed to the revision of the manuscript. Ajay Kodiyatar supported the study methodology, benchtop procedures and manuscript preparation. Megh Singh Dhakad assisted with the statistical analysis and data interpretation. BC Koner reviewed and finalized the manuscript prior to submission. Niket Rai supervised the overall research direction and provided oversight throughout the study.

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Declaration of conflicting interests: No conflicts of interest.

Animal Ethics Consent: This study was conducted at the Central Animal Facility and Department of Pharmacology, Maulana Azad Medical College (MAMC), New Delhi. Ethical approval was obtained from the Institutional Animal Ethics Committee (IAEC) under approval number IAEC/MAMC/CAF/2023/03, dated 28-04-2023

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Tables and Figures:

Table 1: Induction of Diabetes (Pre-treatment Data)

Group	Weight (g) (Baseline)	Weight (g) (Day 0)	FBG (mg/dL) (Day 0)
NC	163.16 ± 9.95	265.83 ± 21.77	101.16 ± 12.78
DC	163.16 ± 6.64	302.83 ± 56.02	476.00 ± 80.88*
Met	158.16 ± 5.38	235.50 ± 22.98	461.50 ± 13.50*
GS	154.66 ± 4.84	269.50 ± 32.77	448.66 ± 10.26*
Met + GS	156.00 ± 6.54	280.16 ± 24.01	436.33 ± 27.78*

*Significantly different from NC ($p < 0.05$); *Data expressed as mean ± SEM; n = 6 per group

Table 2: Effects of Treatments on Day 28

Group	Weight (gm)	FBG (mg/dl)		Cholesterol (g/L)		Creatinine (mg/dl)		Hb1Ac (g/L)	
	Day 28	Day 7	Day 28	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28
DC	293.0 ±	445.66 ±	401.33 ±	351.6 ±	345.14 ±	2.05 ±	1.85±	10.55 ±	9.95 ±

	33.41	51.74	24.548	75.99	70.77	0.47	0.04	0.57	0.49
Met	389.8 ± 19.53*	409.66 ± 8.16*	122.50 ± 6.15*	331.6 ± 10.06	106.49 ± 2.73*	1.85 ± 0.76	0.44 ± 0.03*	10.65 ± 0.11	5.82 ± 0.15*
GS	393.0 ± 30.21*	423.83 ± 13.61	296.33 ± 8.26*†	323.9 ± 16.91	293.43 ± 3.29*†	1.77 ± 0.89	0.69 ± 0.04*†	10.62 ± 0.27	8.24 ± 0.13*†
Met+ GS	421.8 ± 27.96*†	395.83 ± 10.88*†	176.50 ± 9.20*†	315.7 ± 14.53	208.99 ± 1.18†	1.74 ± 0.12	0.54 ± 0.02*†	10.65 ± 0.70	7.26 ± 0.09*†

*Significant vs. DC ($p < 0.05$)

†Significant vs. Met ($p < 0.05$)

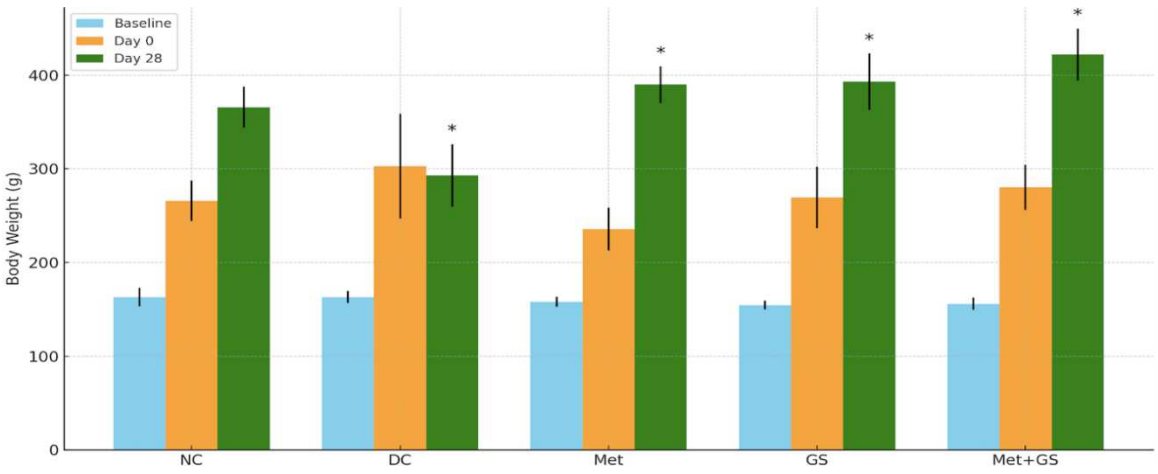


Figure 1: Body Weight at Baseline, Day 0, and Day 28

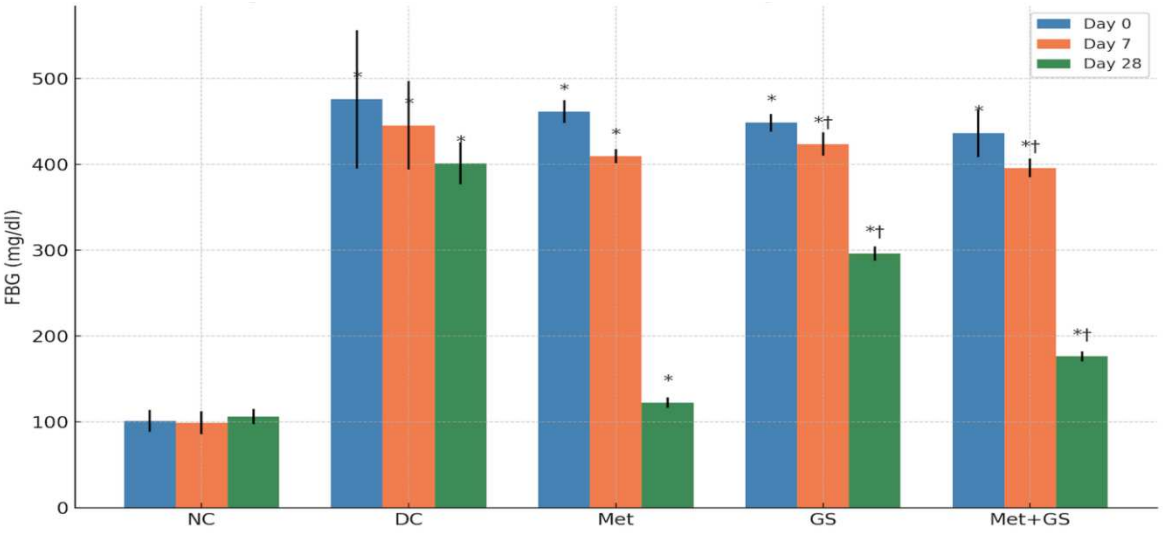


Figure 2: FBG (mg/dl) at Day 0, Day 7, and Day 28

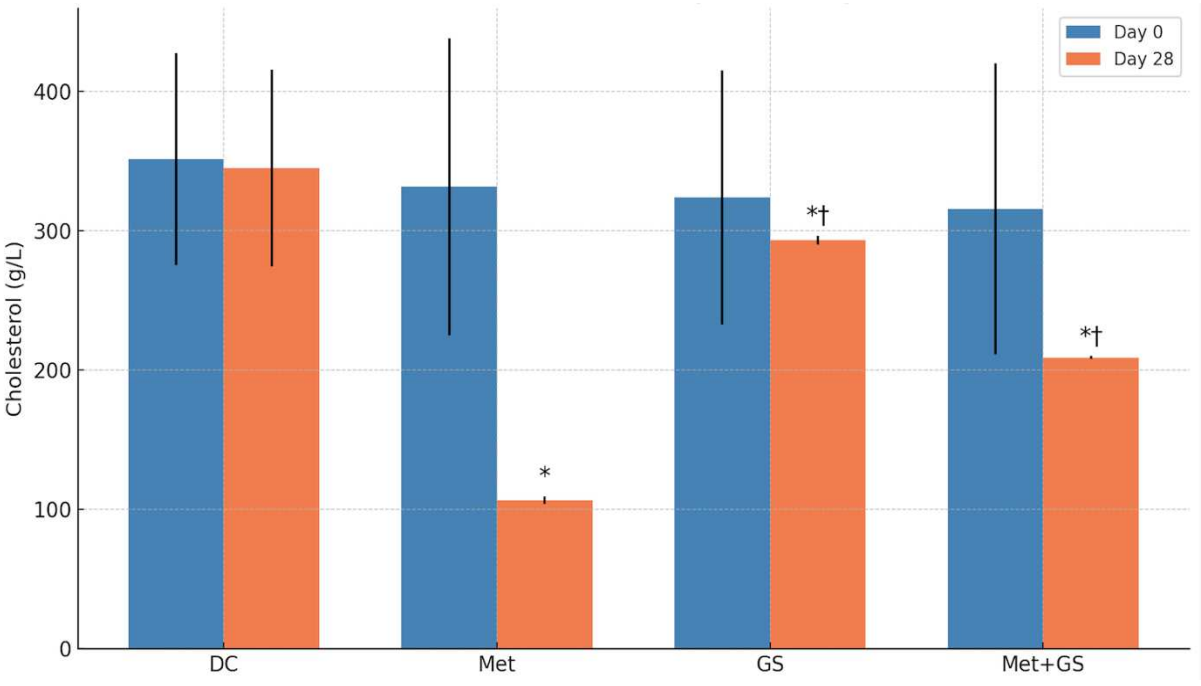


Figure 3: Cholesterol (g/L) at Day 0 and Day 28

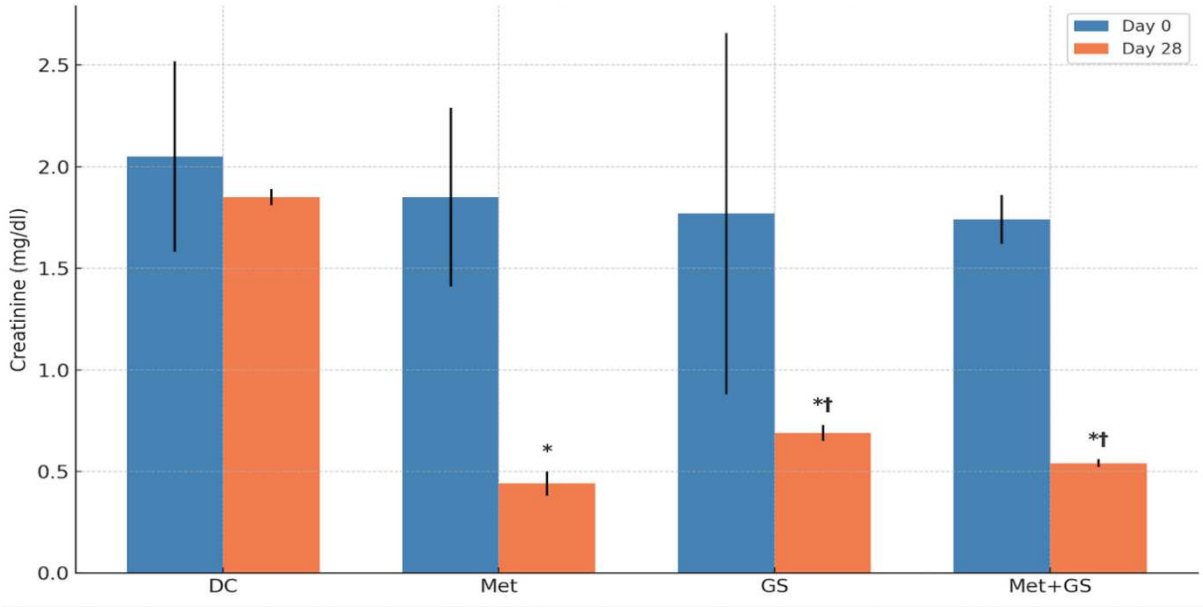


Figure 4: Creatinine (mg/dl) at Day 0 and Day 28

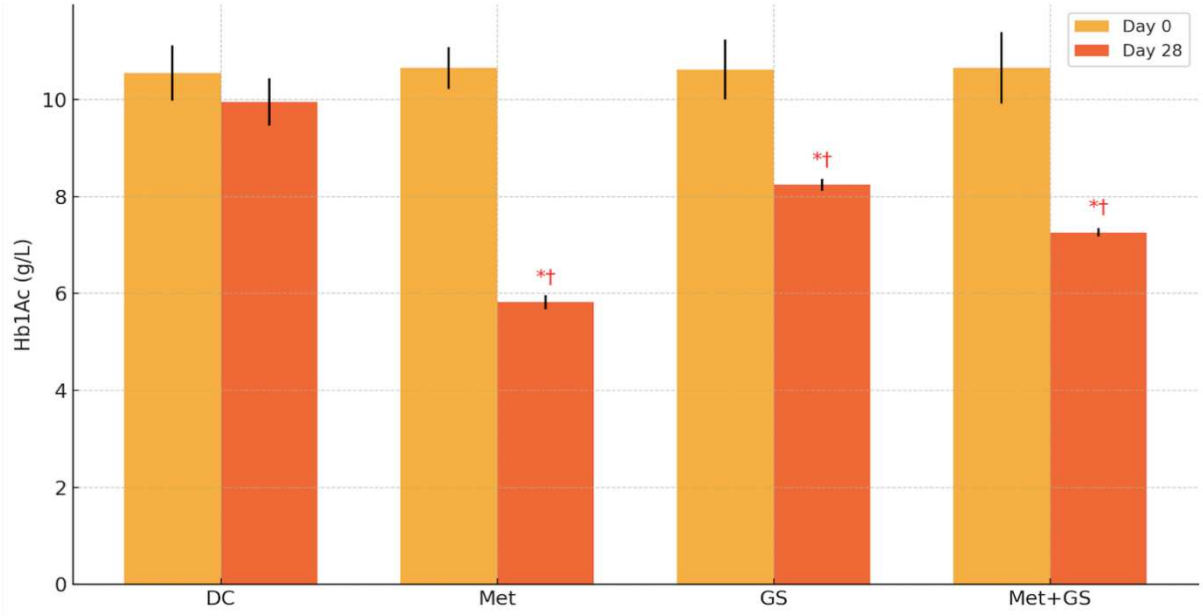


Figure 5: HbA1c (g/L) at Day 0 and Day 28

Figures

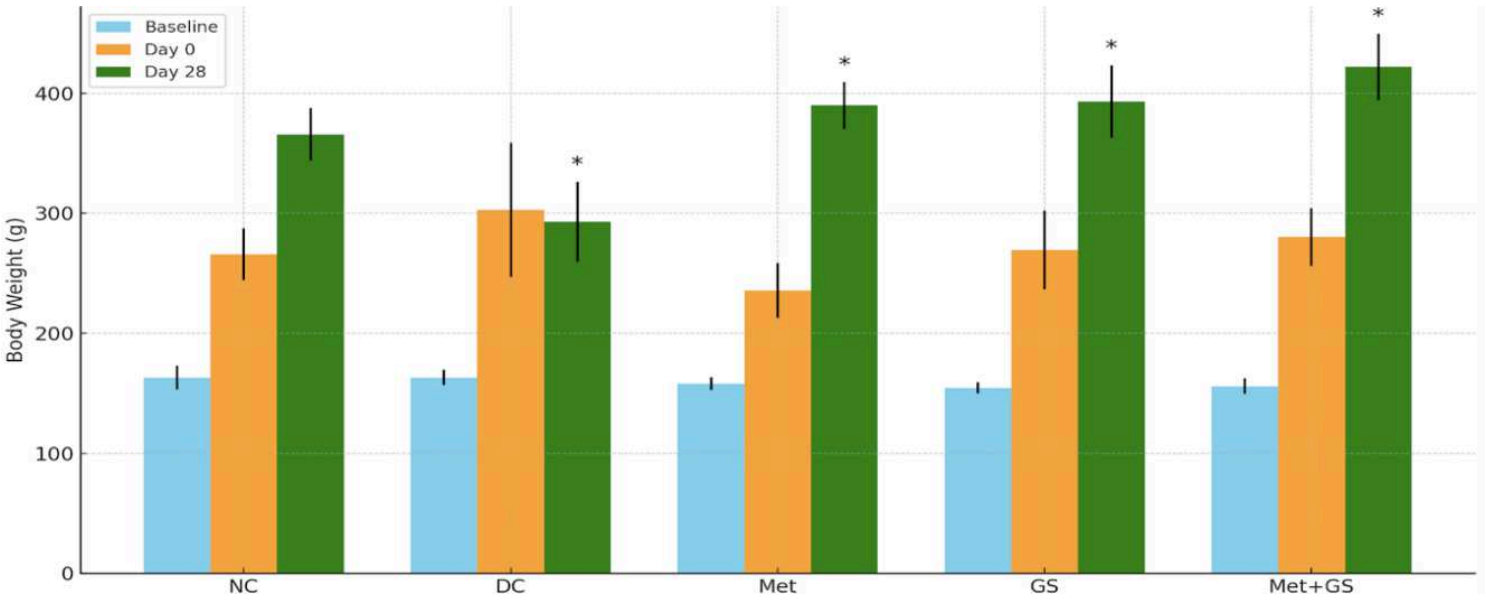


Figure 1

Body Weight at Baseline, Day 0, and Day 28

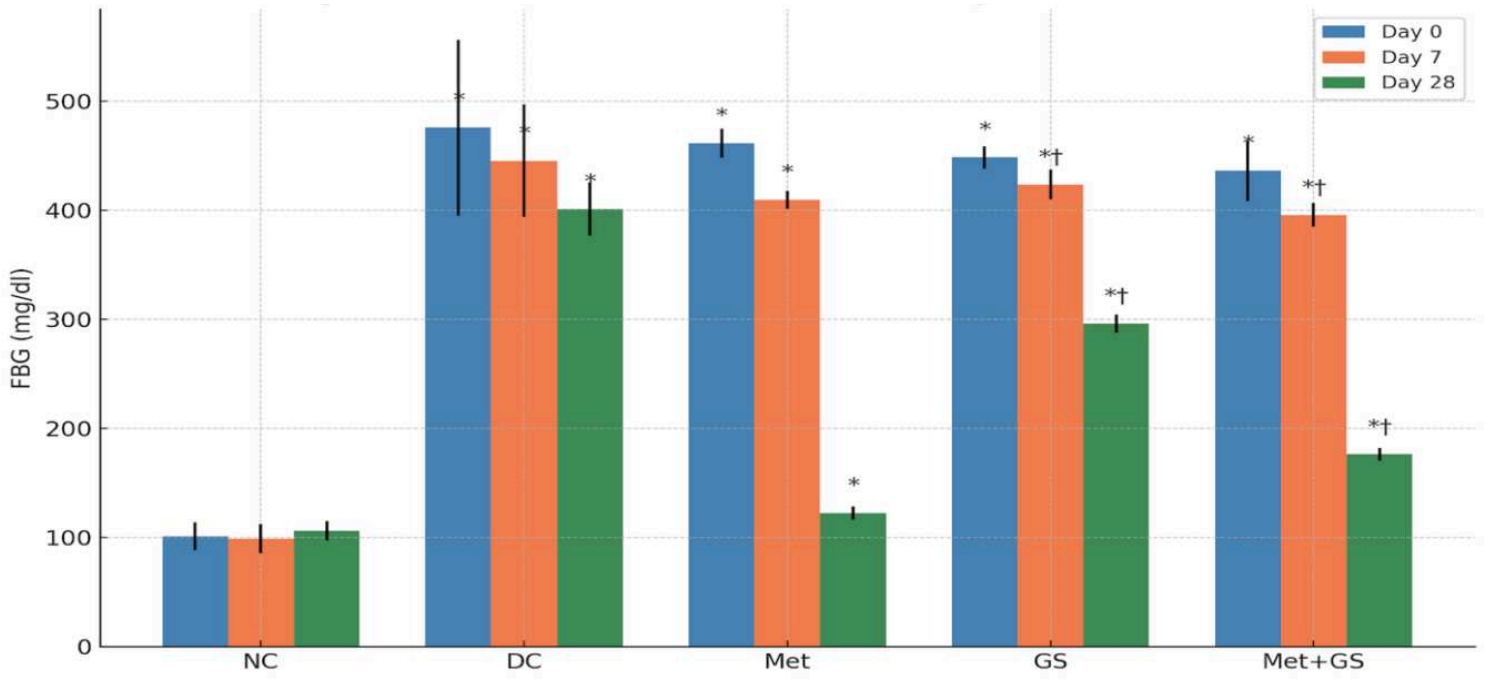


Figure 2

FBG (mg/dl) at Day 0, Day 7, and Day 28

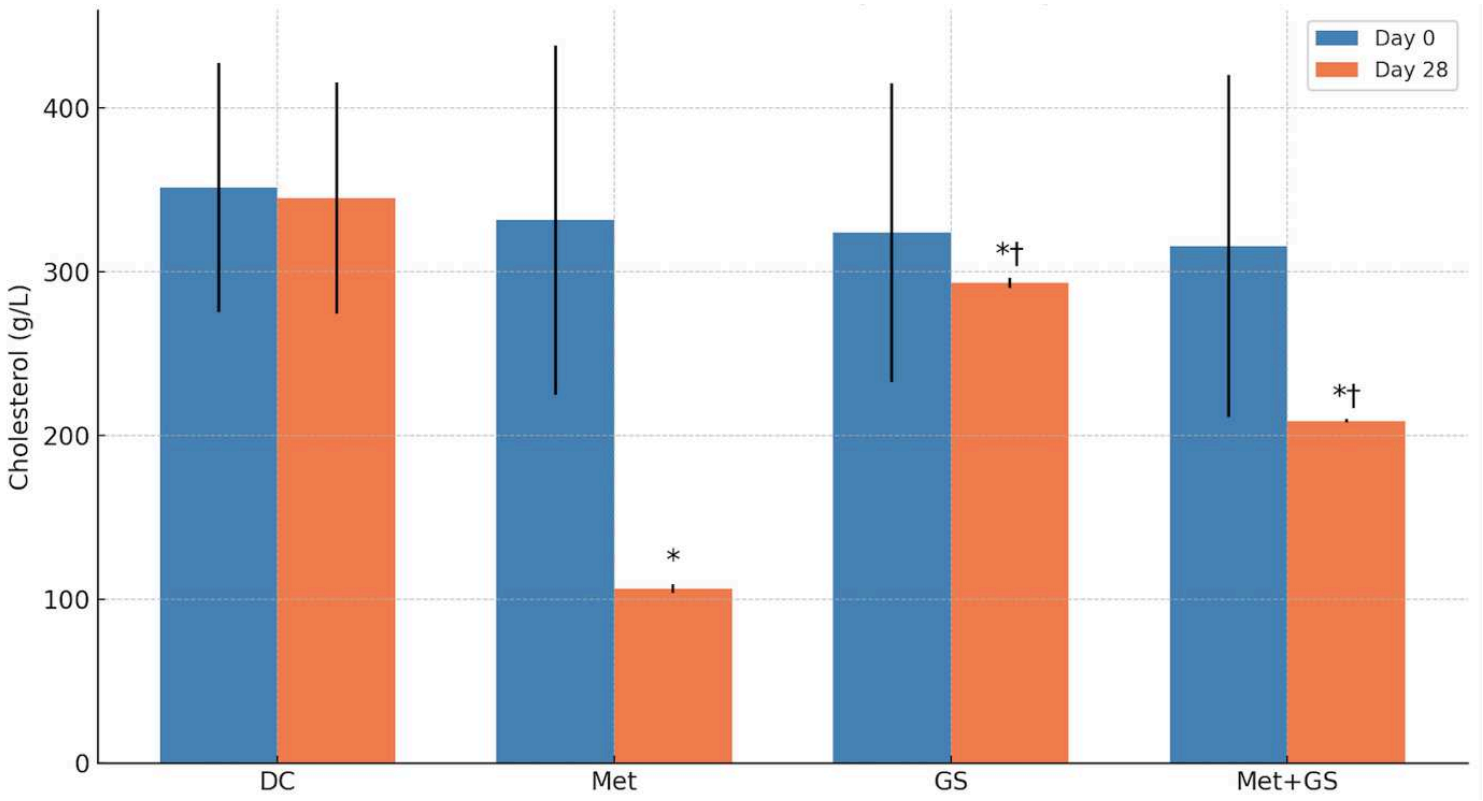


Figure 3

Cholesterol (g/L) at Day 0 and Day 28

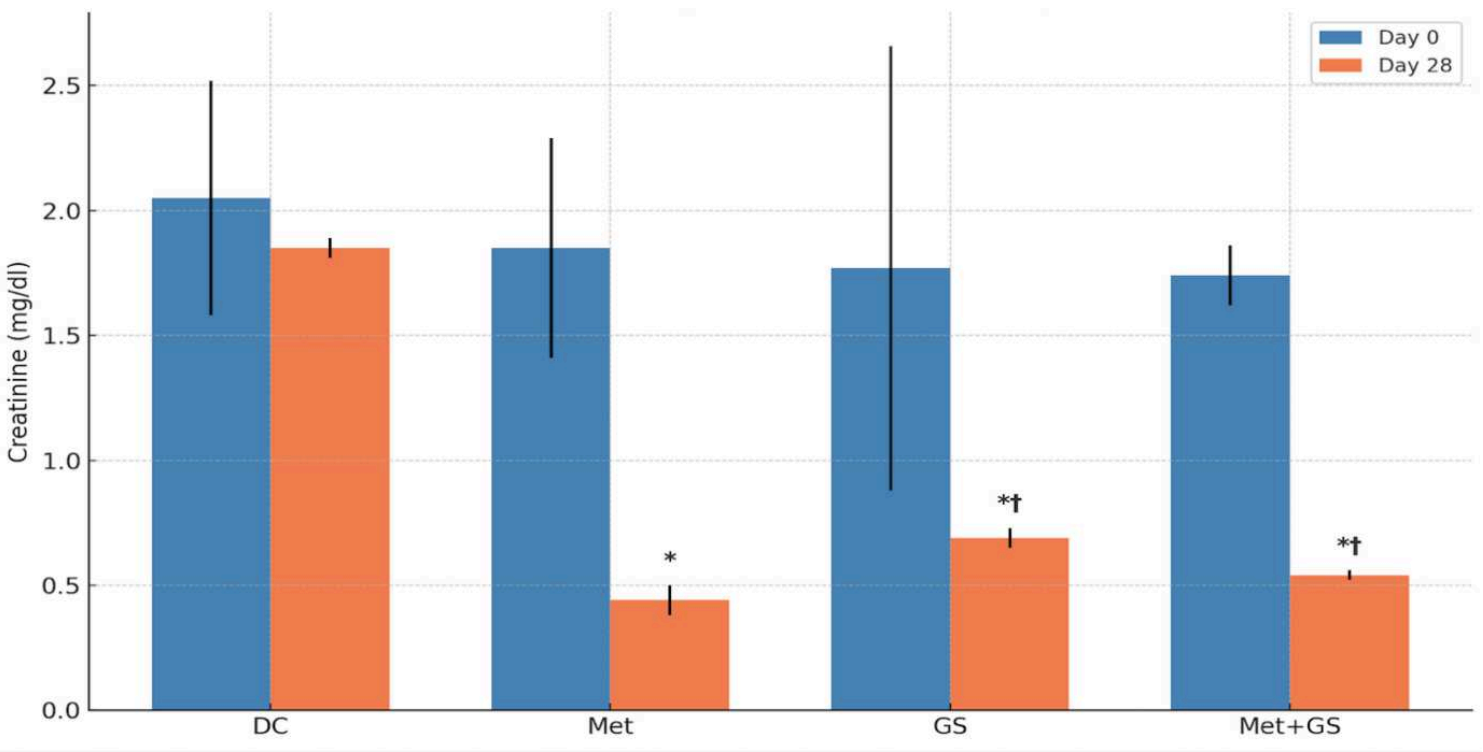


Figure 4

Creatinine (mg/dl) at Day 0 and Day 28

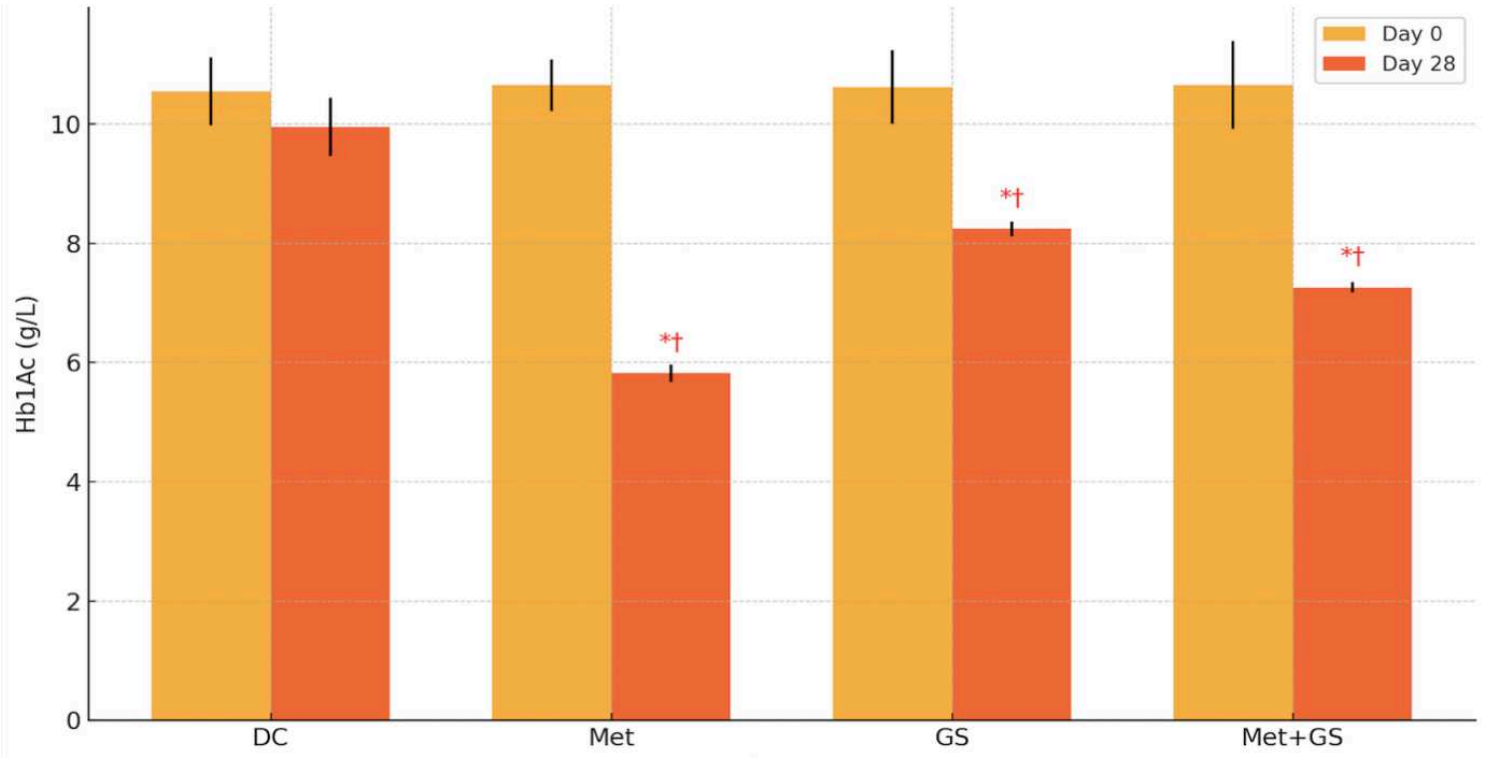


Figure 5

HbA1c (g/L) at Day 0 and Day 28