



Evaluation of Anti-diabetic Activity of Vonoprazan and its Synergistic Effect with Metformin in Streptozotocin Induced Diabetes in Rats.

Mohammed A. N. Abbas^{1*}, Mohammed A. Alkhawlan², Hassan Al-Muhibishi¹, Abdunaser S. A. Aklan¹, Khaled Alhumaidha¹, Abdullah A. A. Ali², Abdullah S.A. Ahmed¹ and Abdul-Malik Abudunia¹

¹Department of Pharmacology & Therapeutics, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a Yemen,

²Department of Medicinal chemistry, Faculty of Pharmacy, Sana'a university, Sana'a, Yemen.

*Corresponding author: mohammed.no2013@gmail.com

ABSTRACT

Background: Vonoprazan, classified as a potassium-competitive acid blocker, suppresses the secretion of gastric acid and indirectly increases circulating gastrin levels through a feedback-mediated mechanism. Recent findings indicate that vonoprazan may influence glucose homeostasis and insulin sensitivity, suggesting a possible role in the modulation of metabolic aberrations, specifically pertaining to the pathophysiology of Type 2 Diabetes Mellitus (T2DM). **Objectives:** The current study was conducted to appraise the anti-diabetic properties of vonoprazan and to assess its combined effect with metformin in a rat model of T2DM established via a high-fat diet (HFD) combined with streptozotocin (STZ). **Methods:** Twenty-five adult male rats were participants randomly assigned to five experimental groups (n=5): normal control, positive control, diabetic rats administered metformin, diabetic rats administered vonoprazan, and diabetic rats subjected to a dual regimen comprising vonoprazan and metformin. After inducing diabetes, the treatments were delivered via oral gavage once daily for four weeks. At the experimental endpoint, blood samples were processed for biochemical assessment. Pancreatic tissues were excised, weighed, and processed for histological evaluation to investigate morphological alteration. **Results:** Administration of vonoprazan, metformin, or their combination significantly improved glycemic indices, as evidenced by reduction in fasting blood glucose (FBG) and insulin resistance. Additionally, treated groups exhibited significant decreases in body weight and dyslipidemic markers, including low-density lipoprotein (LDL), total cholesterol (TC), and triglyceride (TG). Conversely, serum insulin concentrations, high-density lipoprotein (HDL) levels, absolute pancreatic mass, and pancreas-to-body weight ratio were significantly elevated compared with the positive control. The combined vonoprazan with metformin regimen demonstrated superior metabolic and histological improvement relative to monotherapy. **Conclusion:** These findings indicate that vonoprazan possesses notable metabolic benefits and potentiates the therapeutic effects of metformin. Therefore, vonoprazan may serve as an emerging ancillary agent in the therapeutic landscape of T2DM, providing a novel pharmacological approach for enhancing glycemic and lipid profile outcomes.

ARTICLE INFO

Keywords:

Vonoprazan, HFD/STZ induced diabetes , Fasting blood glucose, Metformin, Insulin resistance HOMA-IR.

Article History:

Received: 29-January-2026,

Revised: 12-April-2026,

Accepted: 17-April-2026,

Published: 28 April 2026.

1. INTRODUCTION

Diabetes mellitus is one of the most critical health crises facing the international community. Recent estimates from the International Diabetes Federation indicate that approximately 589 million individuals will be affected glob-

ally in 2024, with the burden expected to rise substantially to nearly 853 million cases by 2050 [1]. This alarming increase underscores the urgent need for improved therapeutic strategies and experimental models to better understand disease progression and interventions. In ex-



perimental research, streptozotocin (STZ) is extensively employed to induce diabetes because of its selective cytotoxicity toward pancreatic β -cells, leading to sustained hyperglycemia. When combined with a high-fat diet (HFD), STZ produces a robust and reproducible animal model that closely mimics the metabolic aberrations that are hallmarks of T2DM, including impaired insulin sensitivity, dyslipidemia, and pancreatic dysfunction [2]. Metformin remains the first-line oral antidiabetic agent for managing and preventing T2DM. Its therapeutic efficacy is primarily attributed to enhanced insulin sensitivity in the hepatic and peripheral tissues, curbing endogenous glucose production in the liver, and facilitating glucose uptake by the skeletal muscle and adipose tissue. These actions collectively contribute to improved glycemic control, particularly when combined with lifestyle modifications [3].

Vonoprazan, a newer generation potassium-competitive acid blocker, has gained significant clinical traction for managing acid-related gastrointestinal disorders. It is extensively utilized in treating gastric and duodenal ulcers, as well as reflux esophagitis, and serves as a pivotal adjunctive component in *Helicobacter pylori* eradication [4]. Mechanistically, vonoprazan exerts its pharmacological effect through the selective and reversible inhibition of the H/K-ATPase pump; it competes with luminal potassium ions essential for the H^+ ion exchange [5]. Notably, clinical evidence indicates that vonoprazan induces a more pronounced elevation in serum gastrin levels than traditional proton pump inhibitors (PPIs), with reported increases ranging from two to three times higher [6].

While the role of gastrin in fostering β -cell regeneration and improving glycemic control is well documented [7], the pharmacological influence of vonoprazan on T2DM remains unexplored. Therefore, this study aimed to assess the potential hypoglycemic and protective effects of vonoprazan in HFD/STZ-induced diabetes. The secondary objective was to explore the therapeutic synergy between vonoprazan and metformin in mitigating insulin resistance and reversing diabetes-associated pancreatic damage. Accordingly, we hypothesized that vonoprazan exerts antihyperglycemic and pancreatic protective effects in HFD/STZ-induced T2DM and synergistically enhances the efficacy of metformin

2. MATERIALS AND METHODS

2.1. DRUGS AND CHEMICALS

Metformin was obtained from Dank Pharma CO. (Germany), and vonoprazan was supplied by Hikma Pharmaceutical CO. (Egypt). All tested drugs were freshly prepared in 0.5% CMC dissolved in distilled water and were administered orally. Streptozotocin (STZ) was obtained from Sigma-Aldrich (St. Louis, MO, USA), and rat insulin (INS) ELISA kits were procured from Elabscience

Biotechnology Co., Ltd. (Wuhan, China). Lipid profile assay kits were procured from Beckman Coulter Ireland Inc. The ingredients of the high-fat diet were sourced from commercial suppliers.

2.2. ANIMALS

Twenty-five adult male albino Wistar rats (weight range: 150–250 g) were procured from the animal facility at the Faculty of Science, Sana'a University. Upon arrival, the rats were subjected to a one-week acclimatization period before the commencement of the experiment. The rats were individually housed in wire-mesh plastic cages. Rats were maintained under standardized laboratory conditions, including a controlled ambient temperature of $25 \pm 2^\circ\text{C}$, relative humidity of $30 \pm 5\%$, and a consistent 12-h light/dark cycle. The rats were provided free access to standard chow and water. All procedures followed ethical guidelines and were sanctioned by the Ethics Committee at the Faculty of Medicine and Health Sciences, Sana'a University, Serial Number (26) 10-10/2026.

2.3. EXPERIMENTAL DESIGN

Upon completion of the acclimatization phase, the rats were randomly allocated into five groups ($n = 5$). Group 1 (Normal control): Administered 0.5% CMC via oral gavage (p.o.). Group 2 (Positive control): Administered 0.5% CMC via oral gavage (P.O.). Group 3 (Metformin group): Administered metformin at a dose of 200 mg/kg/day orally [8, 9]. Group 4 (Vonoprazan group): Administered vonoprazan at a dose of 20 mg/kg (p.o.) [10]. Group 5 (Combination group): Administered a concomitant dose of metformin (200 mg/kg) and vonoprazan (20 mg/kg) (p.o.). The experimental treatments were administered daily over a four-week duration. Rats underwent weekly assessments of their body weight and FBG concentrations. FBG concentrations were checked by taking blood from the caudal vein and testing it with a portable Accu-Chek Active device (Roche Diagnostics). Following the completion of the experimental duration, rats were anesthetized using a ketamine-xylazine mixture (80/10 mg/kg) as previously described [11]. Blood samples were harvested via cardiac puncture and processed by centrifugation. The resulting serum was cryopreserved at -80°C . Subsequent to blood harvesting, euthanasia was carried out by cervical dislocation, and pancreatic tissues were excised, weighed, and fixed for histological evaluation.

2.4. INDUCTION OF TYPE 2 DIABETES MELLITUS

The T2DM model was established following the protocol described by [12] with minor modifications. Initially, rat models were maintained on a high-fat diet made up of 17% carbohydrates, 25% proteins, and 58% fats—for a

period of three weeks ad libitum. Following the dietary priming, the rats were subjected to an overnight fast and subsequently administered a single intraperitoneal (i.p.) injection of streptozotocin (STZ) 35 mg/kg body weight [12]. The STZ was freshly dissolved in a 0.1 mM citrate buffer (pH 4.5) and delivered in a volume of 2 mL/kg. To confirm the induction of diabetes, fasting blood glucose (FBG) levels were monitored 72 hours post-injection via caudal-vein sampling using an Accu-Chek Active device. Animals exhibiting FBG levels exceeding 200 mg/kg were classified as diabetic and included in the study [13]. The control group consisted of healthy rats fed a standard dietary regimen and administered a vehicle (citrate buffer) injection. Pharmacological intervention commenced on the 7th day post-STZ injection. The test drugs were administered daily via oral gavage for a duration of four weeks. During this period, all rats were fed with normal pellets only and water.

2.5. ASSESSMENT OF BODY WEIGHT AND PANCREATIC PARAMETERS:

Body weight was recorded at baseline and at the end of the experimental period using a digital balance to determine weight change. Following euthanasia, the pancreas was immediately excised and weighed. The pancreas-to-body weight ratio was calculated and expressed as a percentage.

2.6. BIOCHEMICAL ANALYSIS

2.6.1. Fasting Blood Glucose

Fasting glycemia was monitored weekly throughout the treatment period. Measurements were obtained from caudal vein blood using a handheld Accu-Chek Active device (Roche Diagnostics), following standard procedures [14].

2.6.2. Fasting blood insulin

Serum insulin concentrations were quantified using a rat-specific (ELISA) kit (Elabscience Biotechnology Co., Ltd.); and measurements were performed strictly according to the manufacturer's instructions.

2.6.3. Insulin resistance index (HOMA-IR)

To assess insulin sensitivity, the HOMA-IR index was employed, integrating fasting glucose and insulin values as defined by the following formula [15]:

$$\text{HOMA-IR} = [\text{FBG (mmol/L)} \times \text{fasting insulin } (\mu\text{U/mL})] / 22.5 \text{ [15].}$$

2.6.4. Lipid profile analysis

LDL-C, HDL-C, total cholesterol, and triglyceride levels were quantified using enzymatic colorimetric methods on Beckman Coulter AU analyzers following the manufacturer's protocols.

2.7. HISTOLOGICAL EXAMINATION

Pancreatic tissues were preserved in 10% phosphate-buffered formalin and processed into paraffin sections. Tissue sections were prepared using hematoxylin and eosin (H&E) staining for histological screening [16]. Microscopic analysis was performed using a light microscope (Olympus CX41) equipped with a CCD digital camera (Olympus SC100). Histopathological evaluation was conducted by an experienced observer who was unaware of the experimental group assignments to prevent observer bias.

2.8. STATISTICAL ANALYSIS:

Quantitative variables are presented as mean $\pm$ SD. For differences across the study groups, a one-way ANOVA was utilized, followed by the LSD post hoc test to identify specific intergroup differences. Results were considered statistically significant if the p-value was less than 0.05. Data processing and analysis were conducted using SPSS software (version 27).

3. RESULTS

3.1. EFFECT OF VONOPRAZAN, METFORMIN, AND THEIR COMBINATION ON BODY WEIGHT AND PANCREATIC PARAMETERS

By the conclusion of the experimental timeframe, a significant decline in body weight was observed in all diabetic cohorts relative to the normal control ($p < 0.05$). Metformin-administered rats showed a pronounced loss of body weight relative to the positive control. In contrast, rats administered vonoprazan alone or in combination with metformin demonstrated a moderate reduction in body weight relative to the positive control (Figure 1), suggesting that vonoprazan may mitigate the excessive weight loss commonly associated with conventional antidiabetic therapy. Regarding pancreatic parameters, the positive control group displayed a significant decline in absolute pancreatic mass and its proportion to total body weight relative to the normal control group ($p < 0.05$). While monotherapy with either metformin or vonoprazan markedly reversed these declines, combined therapy with both agents demonstrated superior efficacy, resulting in better preservation of the pancreatic mass and its proportion to total body weight compared with either monotherapy (Figure 2).

3.2. EFFECT OF VONOPRAZAN, METFORMIN, AND THEIR COMBINATION ON FASTING BLOOD GLUCOSE.

Following diabetes induction and prior to pharmacological intervention (week 0), all diabetic groups exhibited a significant elevation in fasting blood glucose (FBG) levels

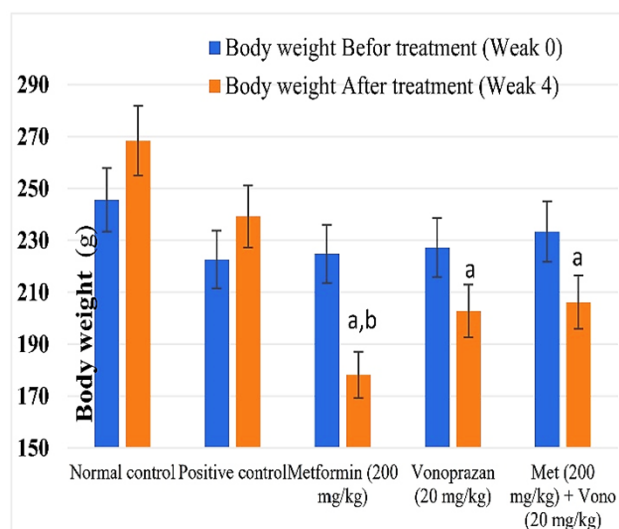


Figure 1. Changes in Body Weight during the Treatment Period: Week 0 (before starting treatment) and Week 4.

Data are presented as the arithmetic mean $\pm$ SD for $n=5$ replicates. Statistical significance ($p < 0.05$) was determined using ANOVA with the LSD post hoc test. **a:** $p < 0.05$ vs. normal control; **b:** $p < 0.05$ vs. positive control.

compared to the normal control ($p < 0.05$). Throughout the four-week treatment period, all treated groups demonstrated a progressive reduction in FBG levels. Over the four-week treatment duration, FBG values in all the treatment groups were significantly lower than those observed in the positive control group ($p < 0.05$). Importantly, the combination of vonoprazan and metformin produced a significantly greater reduction in FBG than either metformin or vonoprazan monotherapy, indicating a synergistic glucose-lowering effect (Figure 3).

3.3. EFFECTS OF VONOPRAZAN, METFORMIN, AND THEIR COMBINATION ON FASTING INSULIN AND HOMA-IR

Serum insulin concentrations were significantly elevated in the positive control group compared to the normal group at the end of the experimental period ($p < 0.05$). Treatment with metformin or vonoprazan alone significantly increased serum insulin levels compared to those in the positive control group. Furthermore, combined treatment with vonoprazan and metformin led to a more pronounced elevation in serum insulin levels. compared with that of the positive control and metformin-treated groups ($p < 0.05$). Additionally, insulin resistance, quantified by HOMA-IR values, was markedly higher in the positive control group than in the normal control group ($p < 0.05$). All treatment regimens significantly reduced HOMA-IR values compared to those in the positive control group. The greatest improvement in insulin sensitivity was observed in the combination therapy group, followed by the vonoprazan monotherapy group, whereas met-

formin alone showed a comparatively modest but significant effect (Figure 4).

3.4. EFFECTS OF VONOPRAZAN, METFORMIN, AND THEIR COMBINATION ON LIPID PROFILE

Dyslipidemia showed significantly higher ($p < 0.05$) cholesterol, triglyceride, and LDL levels and reduced HDL levels in the positive control compared to the normal control.

Significant favorable shifts in lipid markers ($p < 0.05$) were observed across all treatment groups.

relative to that of the positive control. The combination group stood out by restoring lipid profiles almost entirely to the baseline levels. Furthermore, metformin monotherapy showed a slight but statistically significant superiority ($p < 0.05$) in reducing TG levels compared with vonoprazan treatment (Figure 5).

3.5. HISTOLOGICAL EXAMINATION

Photomicrograph of the pancreatic tissue of a normal rat showing **(A)** normal histological structure of the general architecture of the pancreatic lobules and the shape and size of the islets of Langerhans. Positive control rat showing **(B)** an abnormality in the general architecture of the pancreatic lobules, with atrophy of the acinar tissue, vascular congestion, inflammatory cell infiltration, and fatty degeneration. The shape and size of the islets of Langerhans were abnormal, with a low number of beta cells showing signs of degeneration and necrosis. Rats treated with metformin **(C)** showed atrophy and necrosis in the acinar cells, mild inflammatory cell infiltration, and fat cells showed marked improvement with the restored size of the islets of Langerhans and a moderate increase in the number of beta cells. Rats treated with vonoprazan **(D)** showed relatively normal acinar cells, with mild vascular congestion, very few inflammatory cell infiltrations, and the shape and size of the islets of Langerhans appeared to be within the normal range, with a moderate increase in the number of beta cells. Rats treated with a combination of vonoprazan and metformin **(E)** showed a normal histological structure of the general architecture of the pancreatic lobules and appeared to maintain their acinar arrangement relatively well. The islets of Langerhans have a normal shape and size. (H.&E.X100).

4. DISCUSSION

Effective management of hyperglycemia is essential to prevent the long-term complications of T2DM. The heterogeneous nature of the disease, involving insulin resistance and β -cell dysfunction, necessitates therapies targeting multiple pathways [17, 18]. The HFD/STZ-induced rat model used in this study reliably reproduced the key

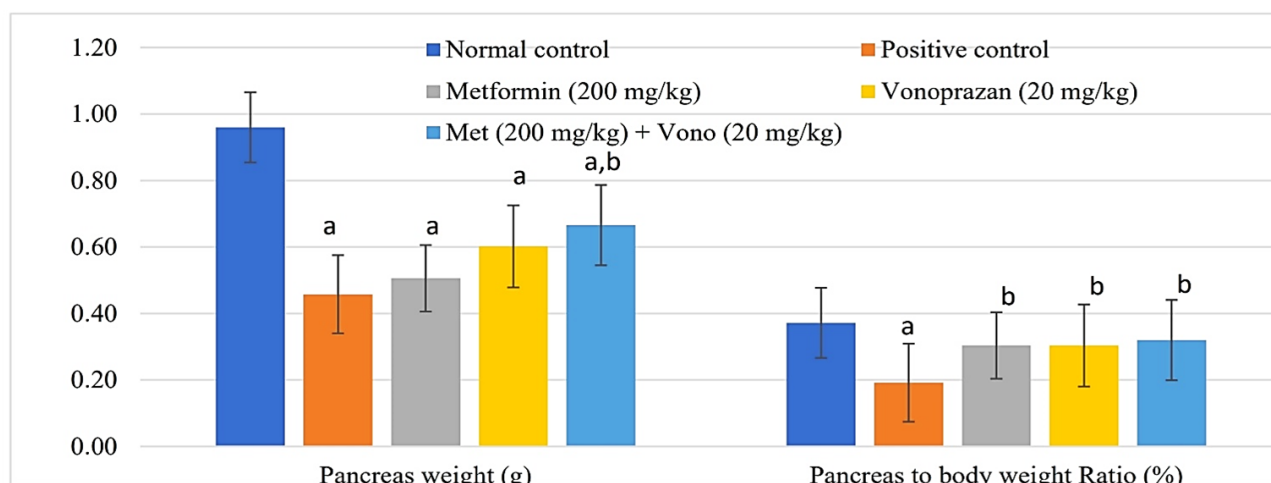


Figure 2. Changes in pancreatic weight and pancreas/body weight ratio at the 4-week post-treatment mark.

Data are presented as the arithmetic mean $\pm$ SD for $n=5$ replicates. Statistical significance ($p < 0.05$) was determined using ANOVA with the LSD post hoc test. **a:** $p < 0.05$ vs. normal control; **b:** $p < 0.05$ vs. positive control.

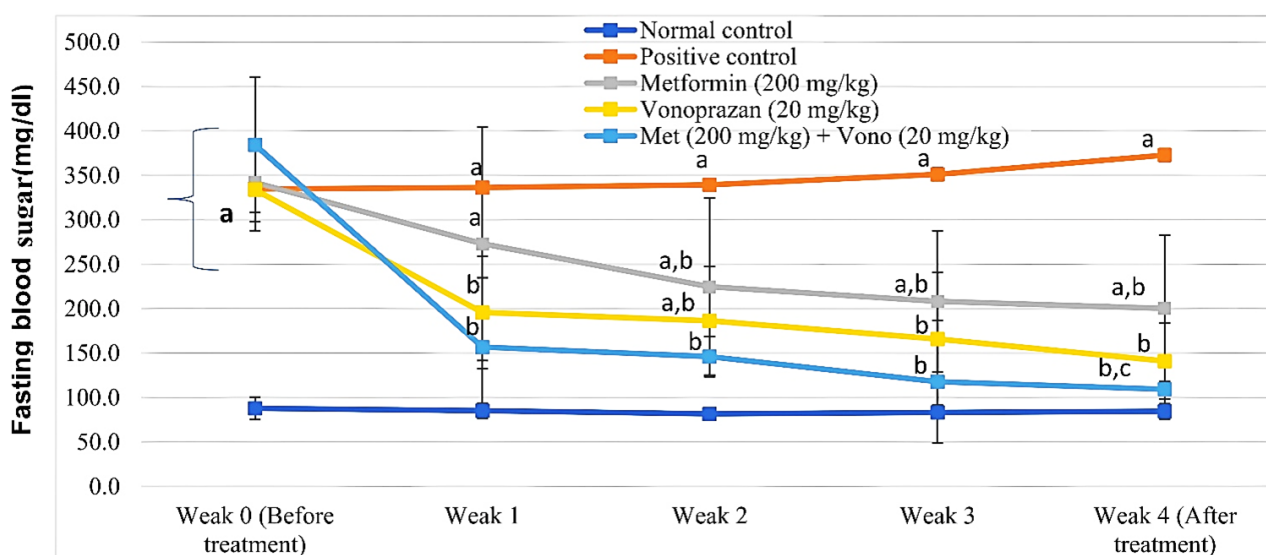


Figure 3. Changes in serum glucose (mg/dl) by study group over the treatment period.

Data are presented as the arithmetic mean $\pm$ SD for $n=5$ replicates. Statistical significance ($p < 0.05$) was determined using ANOVA with the LSD post hoc test. **a:** $p < 0.05$ vs. normal control; **b:** $p < 0.05$ vs. positive control; **c:** $p < 0.05$ vs. metformin group.

features of human T2DM, including hyperglycemia, dyslipidemia, and insulin resistance, validating its use for evaluating antidiabetic interventions [12, 19].

The most notable finding of this study was the superior metabolic improvement observed with the combined administration of vonoprazan and metformin compared with either fasting blood glucose, insulin resistance, or dyslipidemia, along with enhanced preservation of pancreatic mass and histological integrity. These outcomes suggest a synergistic interaction between the two agents that extends beyond their individual pharmacological effects. Alterations in body weight are common features of insulin resistance and diabetes. In agreement with previous studies, untreated

HFD/STZ rats exhibit abnormal weight changes associated with disrupted energy balance and adipose tissue expansion [20, 21].

Metformin monotherapy significantly reduced body weight, a well-documented effect attributed to improved insulin sensitivity and reduced hepatic gluconeogenesis [22].

In contrast, vonoprazan alone induced only modest weight changes that did not reach statistical significance. However, vonoprazan appeared to stabilize body weight and attenuate the excessive catabolic state and cachexia often observed in advanced diabetes models [12, 23]. This stabilization may reflect improved metabolic efficiency rather than direct weight loss and suggests a

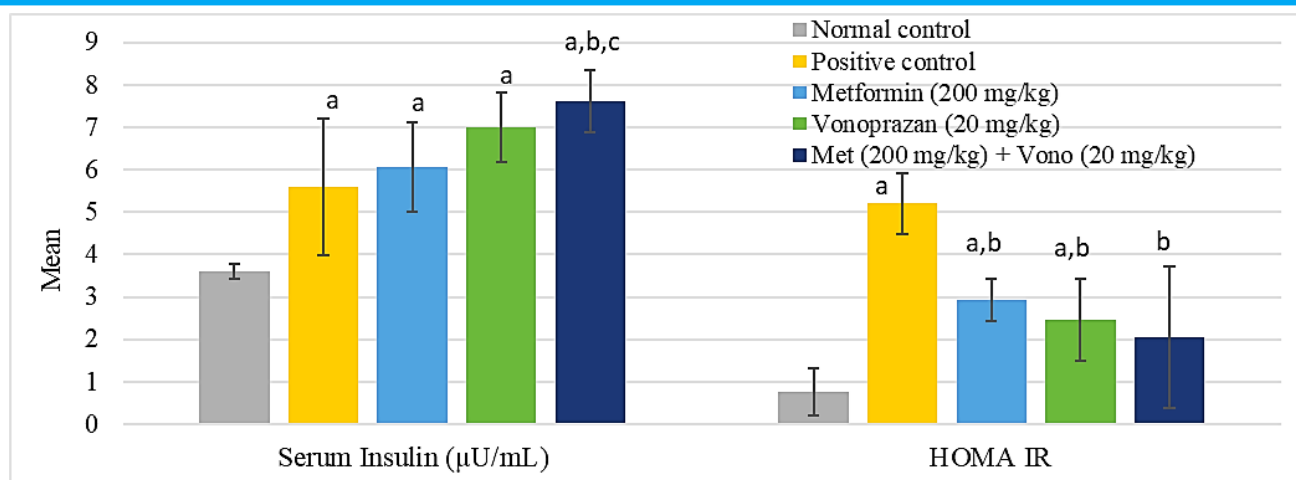


Figure 4. Comparison of serum insulin and HOMA-IR levels among study groups at the 4-week post-treatment mark.

Data are presented as the arithmetic mean $\pm$ SD for n=5 replicates. Statistical significance ($p < 0.05$) was determined using ANOVA with the LSD post hoc test. **a:** $p < 0.05$ vs. normal control; **b:** $p < 0.05$ vs. positive control; **c:** $p < 0.05$ vs. metformin group.

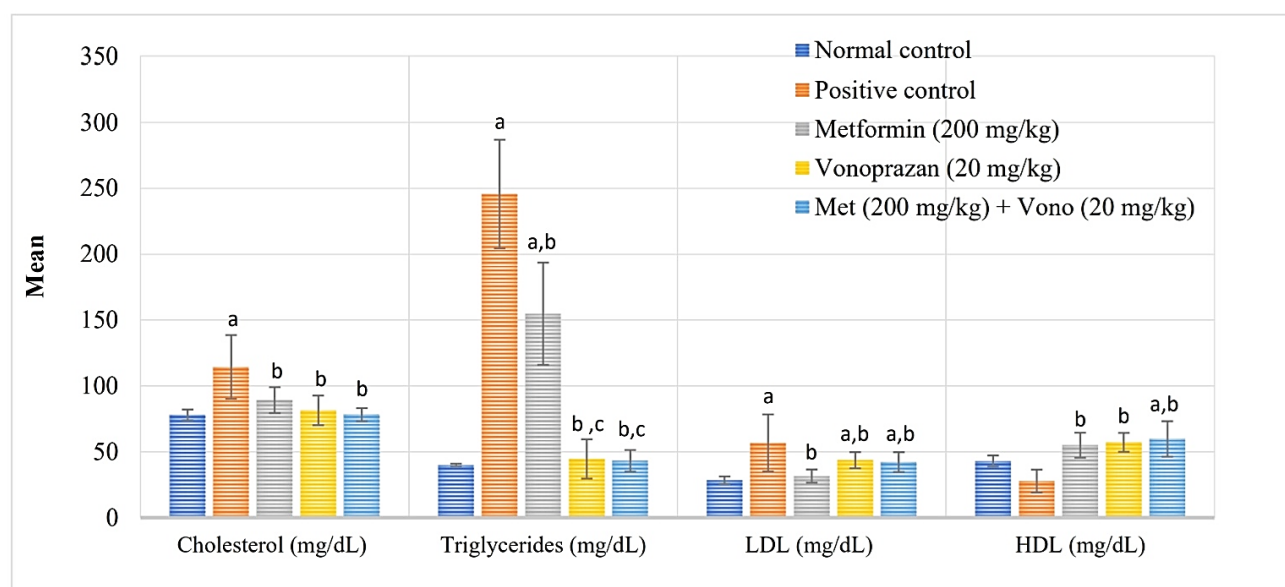


Figure 5. Comparison of lipid profile among study groups at the 4-week post-treatment mark.

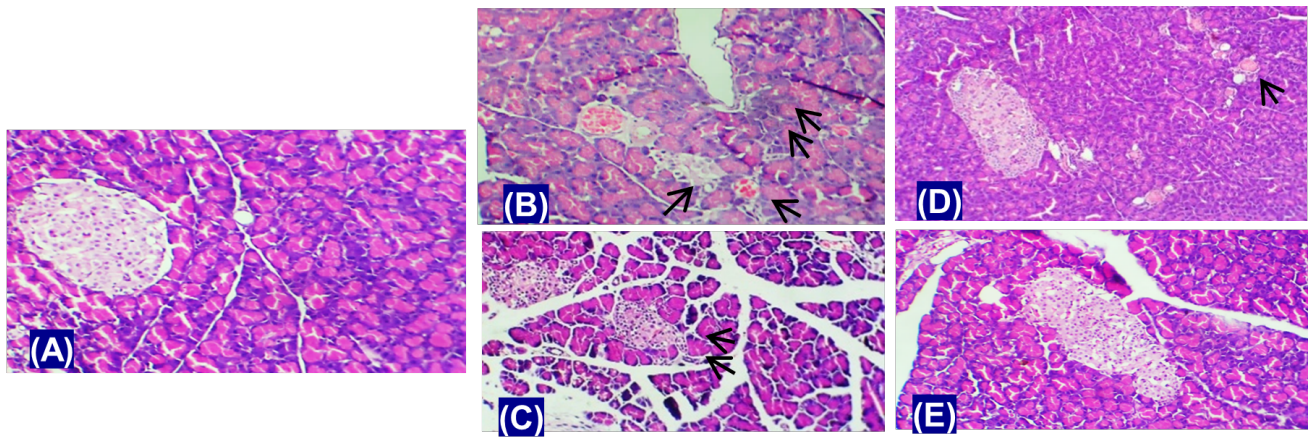
Data are presented as the arithmetic mean $\pm$ SD for n=5 replicates. Statistical significance ($p < 0.05$) was determined using ANOVA with the LSD post hoc test. **a:** $p < 0.05$ vs. normal control; **b:** $p < 0.05$ vs. positive control; **c:** $p < 0.05$ vs. metformin group.

potential role for vonoprazan in maintaining energy homeostasis under diabetic conditions [24].

Nevertheless, further studies are warranted to clarify whether this effect is mediated through enhanced glycemic control and modulation of appetite, delayed gastric emptying, or other indirect mechanisms [25, 26].

Pancreatic atrophy and reduced pancreas-to-body weight ratio observed in positive control rats are consistent with progressive β -cell loss and exocrine pancreatic damage reported in T2DM [27, 28]. While monotherapy with either metformin or vonoprazan produced limited improvements in pancreatic mass, their combined administration resulted in a statistically

significant restoration of pancreatic weight and relative pancreatic index. This finding highlights the potential advantage of combination therapy in preserving pancreatic structure. In the present study, diabetes induction led to marked hyperglycemia and impaired glucose regulation, which were significantly ameliorated by pharmacological intervention. Both metformin and vonoprazan independently improved fasting blood glucose levels, with the combination therapy exerting the most pronounced effect. This enhanced efficacy may be explained by complementary mechanisms of action: metformin primarily improves peripheral insulin sensitivity and suppresses hepatic glucose



production [29], the observed metabolic effects of vonoprazan may be partially attributed to its ability to elevate circulating gastrin levels [30]. Gastrin has been shown to stimulate pancreatic β -cell regeneration and enhance insulin secretion. Additionally, indirect effects on gastric emptying and nutrient absorption may contribute to improved glycemic control [25, 26]. These mechanisms may explain the enhanced efficacy observed when vonoprazan is combined with metformin, a hormone implicated in β -cell proliferation, neogenesis, and insulin secretion [31]. Targeting both insulin resistance and β -cell function simultaneously may therefore account for the superior glycemic control observed with combination therapy. Insulin resistance, assessed by HOMA-IR, was markedly elevated in positive control rats, confirming the successful induction of metabolic dysfunction [32, 33].

All treatment groups exhibited significant reductions in HOMA-IR, with combination therapy achieving the greatest improvement. This finding underscores the capacity of combined pharmacological approaches to address both insulin sensitivity and secretory defects, thereby restoring metabolic balance more effectively than single-agent therapy [32]. Lipid metabolism disturbances are closely associated with insulin resistance and play a pivotal role in the progression of T2DM [34]. In this study, the positive control rats developed severe dyslipidemia, characterized by elevated triglyceride, total cholesterol, and LDL-C levels, accompanied by reduced HDL-C levels. These alterations were significantly improved by pharmacological treatment, with near-normalization observed in the combination therapy group. Vonoprazan monotherapy produced modest yet significant improvements in LDL-C, a finding consistent with clinical observations that glycemic control alone does not always translate into complete lipid normalization in patients [35, 36].

This suggests that vonoprazan may exert additional metabolic effects that warrant further investigation.

Histopathological analysis supported these biochemical findings. Diabetic control rats exhibited severe pancreatic

damage, including acinar atrophy, inflammatory infiltration, and β -cell loss. Monotherapy partially ameliorated these changes, whereas combination therapy nearly restored normal pancreatic architecture and islet integrity, aligning with improvements in insulin secretion and lipid profiles [37, 38].

Limitation

A limitation of this study is its small sample size ($n=5$ per group), which may reduce statistical power and limit the generalizability of the results. Further studies with larger sample sizes are required to confirm these findings.

Conclusion

The present study underscores the potent antidiabetic efficacy of vonoprazan, characterized by significant improvements in glycemic control, HOMA-IR, insulin levels, lipid profile, and body weight in rats. It also enhanced pancreatic mass and pancreas-to-body weight ratio compared to metformin alone. Notably, the combination of vonoprazan and metformin yielded superior outcomes, suggesting that vonoprazan may serve as an effective adjunct to conventional T2DM therapy.

REFERENCES

- [1] International Diabetes Federation, *IDF Diabetes Atlas*, Available: <http://www.diabetesatlas.org/>, Brussels, Belgium, 2025.
- [2] D. A. Magalhaes et al., "High-fat diet and streptozotocin in the induction of type 2 diabetes mellitus: A new proposal," *Anais da Acad. Brasileira de Ciencias*, vol. 91, no. 1, e20180314, 2019.
- [3] U. Hostalek, M. Gwilt, and S. Hildemann, "Therapeutic use of metformin in prediabetes and diabetes prevention," *Drugs*, vol. 75, no. 10, pp. 1071–1094, 2015.
- [4] S. Shinozaki et al., "Long-term vonoprazan therapy is effective for controlling symptomatic proton pump inhibitor-resistant gastroesophageal reflux disease," *Biomed. Reports*, vol. 14, no. 3, p. 32, 2021.
- [5] Y. Abdel-Aziz, D. C. Metz, and C. W. Howden, "Potassium-competitive acid blockers for the treatment of acid-related disorders," *Aliment. Pharmacol. & Ther.*, vol. 53, no. 7, pp. 794–809, 2021.



- [6] H. Echizen, "The first-in-class potassium-competitive acid blocker, vonoprazan fumarate: Pharmacokinetic and pharmacodynamic considerations," *Clin. Pharmacokinet.*, vol. 55, no. 4, pp. 409–418, 2016.
- [7] N. Tellez, G. Joanny, J. Escoriza, M. Vilaseca, and E. Montanya, "Gastrin treatment stimulates β -cell regeneration and improves glucose tolerance in pancreatectomized rats," *Endocrinology*, vol. 152, no. 7, pp. 2580–2588, 2011.
- [8] C. Mega et al., "Biochemical and histological effects of sitagliptin on Zucker diabetic fatty rat pancreas," *Virchows Arch.*, vol. 457, no. 3, pp. 271–281, 2010.
- [9] N. A. Mohamed, S. A. Zaitone, and Y. M. Moustafa, "Effect of sitagliptin in combination with glimepiride on glycemic control and islet cell proliferation in type 2 diabetic rats," *IOSR J. Pharm.*, vol. 3, no. 1, pp. 72–80, 2013.
- [10] F. Chen et al., "Effects of vonoprazan on the pharmacokinetics of venlafaxine in vitro and in vivo," *Drug Des. Dev. Ther.*, vol. 18, pp. 2931–2942, 2024.
- [11] A. Tsukamoto, N. Niino, M. Sakamoto, R. Ohtani, and T. Inomata, "The validity of anesthetic protocols for castration in rats," *Exp. Animals*, vol. 67, no. 3, pp. 329–336, 2018.
- [12] K. Srinivasan, B. Viswanad, L. Asrat, C. L. Kaul, and P. Ramarao, "Combination of high-fat diet-fed and low-dose streptozotocin-treated rat as a model for type 2 diabetes," *Pharmacol. Res.*, vol. 52, no. 4, pp. 313–320, 2005.
- [13] M. Schaalan, H. S. El-abhar, M. Barakat, and E. S. El-Dentary, "Study on diabetes complications," *J. Diabetes its Complicat.*, vol. 23, no. 3, pp. 199–205, 2009.
- [14] M. S. Lamiaa, A. A. Morsi, E. El Bana, and S. M. Hanafy, "Biological impacts of sitagliptin on pancreas in diabetic rats," *Biology*, vol. 9, no. 1, p. 6, 2019.
- [15] X. Guo, Y. Wang, K. Wang, B. Ji, and F. Zhou, "Stability of a type 2 diabetes rat model induced by high-fat diet and streptozotocin," *J. Zhejiang Univ. Sci. B*, vol. 19, no. 7, pp. 559–569, 2018.
- [16] R. A. Drury, E. A. Wallington, and R. Cancerson, *Carlton's Histopathological Techniques*, 4th ed. London: New York University Press, 1976, pp. 279–280.
- [17] S. E. Kahn, M. E. Cooper, and S. Del Prato, "Pathophysiology and treatment of type 2 diabetes," *The Lancet*, vol. 383, no. 9922, pp. 1068–1083, 2014.
- [18] R. A. DeFronzo, "Pathogenesis of type 2 diabetes mellitus," in *Diabetes: Epidemiology, Genetics, Pathogenesis, Diagnosis, Prevention, and Treatment*, 2018, pp. 181–253.
- [19] M. Yokono and et al., "Effect of antidiabetic agents in rodent models," *Eur. J. Pharmacol.*, vol. 727, pp. 66–74, 2014.
- [20] S. I. R. Okoduwa and et al., "Ethnomedicinal plant-based antidiabetic research in Nigeria," *PLoS One*, vol. 12, no. 1, p. 21, 2017.
- [21] J. Y. Lee and et al., "Tnf- α mediates downregulation of adiponectin," *Biochem. Biophys. Res. Commun.*, vol. 407, no. 4, pp. 818–823, 2011.
- [22] W. S. Lv and et al., "Effect of metformin on food intake in obese diabetic rats," *Brain Res.*, vol. 1444, pp. 11–19, 2012.
- [23] B. L. Furman, "Streptozotocin-induced diabetic models in rodents," *Protoc. Pharmacol.*, vol. 70, pp. 5.47.1–5.47.20, 2015.
- [24] C. J. Bailey and S. L. Turner, "Metformin," *New Engl. J. Med.*, vol. 334, no. 9, pp. 574–579, 1996.
- [25] Y. Yoda and et al., "Vonoprazan delays gastric emptying in rats," *J. Physiol. Pharmacol.*, vol. 61, no. 3, pp. 287–294, 2010.
- [26] P. J. B. Millar and et al., "Anti-diabetic effects of proton pump inhibitors," *Mol. Cell. Endocrinol.*, vol. 420, pp. 37–45, 2016.
- [27] J. Zhou, S. Zhou, and S. Zeng, "Experimental diabetes treated with trigonelline," *Fundam. & Clin. Pharmacol.*, vol. 27, no. 3, pp. 279–287, 2013.
- [28] J. Zhuo and et al., "Evaluation of type 2 diabetic animal models," *Mol. Med. Reports*, vol. 17, no. 4, pp. 5132–5142, 2018.
- [29] G. Rena, D. G. Hardie, and E. R. Pearson, "Mechanisms of action of metformin," *Diabetologia*, vol. 60, no. 9, pp. 1577–1585, 2017.
- [30] H. Echizen, "Vonoprazan pharmacokinetics and pharmacodynamics," *Clin. Pharmacokinet.*, vol. 55, no. 4, pp. 409–418, 2016.
- [31] I. Rooman and et al., "Gastrin stimulates beta-cell neogenesis," *Diabetes*, vol. 51, no. 3, pp. 686–690, 2002.
- [32] M. I. Saad and et al., "Modulation of adipocytokines by antidiabetic drugs," *Biochem. Res. Int.*, p. 138 134, 2015.
- [33] P. J. Antony and et al., "Myoinositol ameliorates diabetes in rats," *Biomed. & Pharmacother.*, vol. 88, pp. 1098–1113, 2017.
- [34] H. Wen and et al., "Fatty acid-induced inflammasome activation interferes with insulin signaling," *Nat. Immunol.*, vol. 12, no. 5, pp. 408–415, 2011.
- [35] T. J. Chahil and H. N. Ginsberg, "Diabetic dyslipidemia," *Endocrinol. Metab. Clin. North Am.*, vol. 35, no. 3, pp. 491–510, 2006.
- [36] A. D. Mooradian, "Dyslipidemia in type 2 diabetes mellitus," *Nat. Clin. Pract. Endocrinol. & Metab.*, vol. 5, no. 3, pp. 150–159, 2009.
- [37] G. R. Gandhi and et al., "Pharmacological study," *Eur. J. Pharmacol.*, vol. 745, p. 201, 2014.
- [38] T. B. Bödvarsdóttir and et al., "Diabetes study," *Diabetologia*, vol. 53, p. 2220, 2010.