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ORIGINAL RESEARCH

Efficacy and Safety of Roflumilast versus Alpha-Lipoic Acid in Type 2 Diabetes with Neuropathy: A Comparative Clinical Study

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Aim: We aimed to evaluate the efficacy and safety of roflumilast compared to alpha-lipoic acid (ALA) in type 2 diabetic patients with diabetic neuropathy.

Methods: In this randomized controlled parallel study, 58 type 2 diabetic patients with diabetic neuropathy were randomly allocated into (Roflumilast group; n=29), which received 500 mcg/day of oral roflumilast and (ALA group; n=29), which received 600 mg/day of oral ALA. At baseline and 12 weeks after intervention, blood samples were collected to assess fasting blood glucose (FBG), glycated hemoglobin (HbA1C), insulin, tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), and neurotensin (NT) levels. Homeostatic Model Assessment of Beta Cell Function (HOMA-1β) and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were calculated. Neuropathic symptoms and neuropathic pain were assessed using the Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ), the Michigan Neuropathy Screening Instrument Examination (MNSIE), and the Douleur Neuropathique-4 (DN4) questionnaire.

Results: After intervention and as compared to baseline, both groups showed significant decreases in HbA1C, FBG, fasting insulin level, HOMA-IR, HOMA-1β, and serum levels of TNF-α, MDA, and neurotensin (P<0.001). The comparison between the two study groups post-treatment indicated that the roflumilast group showed a significant decrease in HbA1C by 0.7% (8.8% relative reduction) compared to 0.3% (3.8% relative reduction) in the ALA group (P<0.001), FBG (P<0.001), fasting insulin level (P=0.012), and HOMA-IR (P<0.001). Similarly, serum MDA level was declined by 0.80 nmol/mL (37.0% reduction) with the roflumilast group versus 0.56 nmol/mL (25.1% reduction) with the ALA group (P=0.003). Post-intervention and compared to baseline data, both groups exhibited significant reductions in neuropathy scores (P<0.001). The comparison between the two study groups after treatment revealed non-significant variations between both groups regarding MNSIQ, MNSIE, and DN4 scores (P>0.05).

Conclusion: Roflumilast may offer superior glycemic and oxidative stress control benefits, though neuropathy symptoms control was comparable to ALA.

Clinicaltrials.gov Id: (NCT 05369793).

Keywords: roflumilast, alpha-lipoic acid, type 2 diabetes, diabetic neuropathy, MNSIQ, MNSIE, DN4

Introduction

In 2021, the global estimate of type 2 diabetes mellitus (T2DM) in adults was 537 million, with an assumption suggesting an increase in its prevalence to be about 700 million by 2045.[1] Type 2 diabetes mellitus (T2DM) results from insulin resistance or inadequate insulin secretion by pancreatic β cells, leading to persistent hyperglycemia with subsequent emergence of microvascular and macrovascular problems.[2,3] Among these, diabetic neuropathy (DN) represents one of the most common and disabling complications, significantly reducing patients' quality of life.[4]

Oxidative stress and inflammation play a central role in the pathogenesis of DN. Polyol, advanced glycation end product (AGE), protein kinase C (PKC), diacylglycerol (DAG), and hexokinase pathways promote demyelination and nerve damage.[5] Inflammatory cytokines, including tumor necrosis factor-α (TNF-α), further contribute to hyperalgesia

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and allodynia, which manifest clinically as neuropathic pain and sensory deficits.[6] Lipid peroxidation products such as malondialdehyde (MDA) and neuropeptides like neurotensin are elevated in DN, reflecting ongoing oxidative and inflammatory injury.[7,8]

Microvascular complications, including diabetic neuropathy (DN), impact both the peripheral and autonomic nerve systems and diminish the patient's quality of life. Diabetic neuropathy (DN), affects the patients' quality of life in various aspects, as they suffer from chronic pain, paresthesia, loss of balance, and the potential of having an ulcer and amputation.[4] Furthermore, most of them have difficulty with sleep, walking ability, lack of energy, and emotional anxiety and depression.[9]

Peripheral diabetic neuropathic symptoms can range from painful to non-painful sensations, and cardiac autonomic neuropathy (CAN), which in turn precipitates cardiac diseases.[10] Although the current treatments, such as anticonvulsants and antidepressants, are used as the first line in the management of diabetic neuropathy, they are used for symptomatic treatment of neuropathic pain, eliciting the need for drugs that modulate the progression of diabetic neuropathy.[11]

Alpha-lipoic acid (ALA) is a prospective therapeutic compound recognized for its antioxidant and anti-inflammatory characteristics. It appears effective against many diseases, including cancer, cardiovascular diseases, and neurodegenerative diseases.[12] It is a free radical scavenger against reactive oxygen species (ROS) and a chelator for metallic ions. Moreover, it plays an essential structural role as a cofactor for multiple mitochondrial bioenergetic enzymes. It promotes intracellular glutathione synthesis and the regeneration of vitamins C and E.[13] Consequently, considering the pathogenetic pathways of diabetic peripheral neuropathy (DPN), ALA has been formulated as a disease-modifying agent, alongside other potential treatment options including γ-linolenic acid (GLA), aldose reductase inhibitors, vascular endothelial growth factors, and protein kinase C-β inhibitors. These therapeutic modalities seek to positively impact the fundamental pathophysiology of diabetic peripheral neuropathy (DPN) rather than only provide symptomatic reduction of diabetic peripheral neuropathy (DPN).[14] The efficacy of ALA has been demonstrated through systematic reviews and meta-analyses, indicating its role in enhancing nerve conduction velocity and mitigating neuropathic symptoms in diabetic peripheral neuropathy.[15]

Roflumilast is an FDA-approved medication for treating moderate to severe chronic obstructive pulmonary disease (COPD). Roflumilast is a phosphodiesterase type-4 enzyme (PDE-4) inhibitor that inhibits inflammation.[16] Roflumilast restores normal liver function and testicular architecture by targeting nuclear factor kappa B (NF-κB) and inositol-requiring enzyme 1 (IRE-1), thereby mitigating the release of stress mediators in rats.[17] A human clinical study showed that roflumilast improved glucose metabolism when administered to 205 newly diagnosed diabetic patients.[18] It has been demonstrated that oral roflumilast treatment improved peripheral insulin sensitivity, reduced energy intake, and lowered total and LDL cholesterol when administered to obese and prediabetic patients.[19]

According to ADA guidelines, despite knowing the natural history of DN, there is a lack of effective treatments that reverse the pathogenic mechanism. Additionally, robust clinical studies are needed to search for disease-modifying agents.[20] To date, no study has directly compared the potential disease-modifying effects of roflumilast, a PDE4 inhibitor with anti-inflammatory properties, against alpha-lipoic acid, an established antioxidant therapy in diabetic neuropathy. Many systematic reviews and meta-analyses showed that ALA alleviated the DN-related symptoms. One of the suggested roles of ALA in DN is the regeneration of antioxidant glutathione, and thus antagonizes the oxidative stress that occurs in DN.[21,22] Therefore, this randomized controlled trial aimed to evaluate the efficacy and safety of roflumilast compared with alpha-lipoic acid in type 2 diabetic patients with diabetic neuropathy.

Patients and Methods

Trial Design

This randomized controlled open-label parallel trial involved 58 patients with type 2 diabetes with diabetic neuropathy.

Study Site

The study was conducted at the Internal Medicine Department at Menoufia University Hospital, Shebein Elkom, Egypt, between August 2022 and October 2024. The research conformed to the ethical principles outlined in the Declaration of

Helsinki, established in 1964. The Research Ethics Committee of Tanta University approved the study (Approval Code: 35420/4/22), as did the Research Ethics Committee of Menoufia University (Approval Code: 6/2022INTM). The research was registered as a clinical trial on ClinicalTrials.gov under ID (NCT 05369793). All participants gave their written informed consent.

Recruitment

Patients were recruited from the Internal Medicine Department at Menoufia University Hospital, Shebein Elkom, Egypt, between August 2022 and October 2024.

Medical history and demographic data (age, sex, medication history, and family history of T2DM) were collected for all patients. All participants underwent a physical examination and anthropometric measurements, including weight, height, and calculation of body mass index (BMI) according to the formula: BMI = [Weight (kg) / Height (m^2)].

Inclusion and Exclusion Criteria

The inclusion criteria were age between 25 and 65 years old, patients diagnosed with T2DM according to the American Diabetes Association (ADA) guidelines[23] who had approximately the same diabetic duration and who were already on vildagliptin/metformin (50 mg/1000 mg) for approximately the same period before running of the study, diabetic patients with diabetic neuropathy based on nerve conduction study, patients with glycated hemoglobin (HbA1C) between 7.5%-8.5%, and patients with body mass index (BMI) between 26–35 kg/m^2. The exclusion criteria were patients with diabetes other than T2DM, patients with immune diseases, patients with morbid obesity (BMI $\geq$ 40 kg/ m^2), patients diagnosed with diseases that may disrupt HbA1C testing, weight, glucose or lipid metabolism, patients with cardiovascular diseases, psychiatric, liver disease (bilirubin>1.5mg) and renal disease with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, patients on enzyme inhibitors or inducers, and patients with low vitamin B12 levels (<400 pmol/L). Pregnant and breastfeeding women were also excluded.

Randomization and Allocation Concealment

The patients were randomized using stratified random sampling into two groups: group 1 (Roflumilast group; n=29), which received roflumilast, and group 2 (Alpha-lipoic acid group; n=29), which received alpha-lipoic acid.

Intervention Details

Group 1 (Roflumilast group; n=29), which received 500 mcg once daily orally of roflumilast (Westbreath® 500 mcg tablet, Western Pharmaceutical Industries, Egypt) for 12 weeks, and group 2 (Alpha-lipoic acid group; n=29), which received 600 mg once daily orally of alpha-lipoic acid (Thiotacid® 600 mg tablets, Eva Pharma, Egypt) for 12 weeks.

Follow-Up and Adherence

During the study duration, roflumilast and alpha-lipoic acid were supplied monthly. We assessed participants' adherence by counting the returned pills and measuring the medication refilling rate. Participants were followed up through weekly telephone calls and through monthly direct meetings during clinic visits to evaluate their compliance and to record any adverse pharmacological effects. Patients were excluded if they were non-adherent to the intervention. Non-adherence was defined as taking less than 90% of the study medication at any month of the study duration. Any observed side effects were reported using the side effects checklist.

Outcomes Measures

At baseline and 12 weeks post-intervention, 10 mL of venous blood was drawn from the antecubital vein of each participant between 8:00 am and 11:00 am, after a 12-hour fast. Blood samples were subsequently centrifuged at 4500 g for 10 minutes. The separated sera were divided into two portions: the first was used for immediate evaluation of liver function (ALT), kidney function (SCr), and fasting blood glucose (FBG). Alanine aminotransferase (ALT) was determined by spectrophotometry, serum creatinine (SCr) was evaluated by the Jaffe reaction, and fasting blood glucose (FBG) was measured using the glucose oxidase method. Moreover, glycated hemoglobin (HbA1C) was quantified using the Fine Care™ FIA Meter (Wondfo, China),

a point-of-care method based on immunofluorescence assay. Vitamin B12 level was determined by electrochemiluminescence (ECL). The second portion of sera was frozen at −80°C to assess the serum levels of tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), neurotensin (NT), and insulin levels using double antibody sandwich ELISA kits according to the manufacturer' instructions (Sun Red Company, Shanghai, China, Catalogue No: 201–12-0083, 201–12-1372, 201–12-1319, 201–12-001, respectively). Furthermore, the estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft and Gault method.[24] Homeostatic Model Assessment of Beta Cell Function (HOMA-1β) was computed using the equation: 360 × fasting insulin (μU/mL) / (fasting glucose "mg/dL" − 63)[25] and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated (fasting insulin × fasting blood glucose "mg/dl")/405.[26]

The clinical outcome was assessed through evaluating the effect of the study medications on diabetic neuropathy as follows:

A. We investigated the effect of roflumilast versus alpha-lipoic acid before and after twelve weeks of therapy using the Michigan Neuropathy Screening Instrument (MNSI) to assess distal symmetrical peripheral neuropathy (DSPN). The project described was supported by Grant Number P30DK020572 (MDRC) from the National Institute of Diabetes and Digestive and Kidney Diseases. We collected the MNSI symptoms score and MNSI physical examination before and at the end of the study.[27,28]

B. In addition, the Douleur Neuropathique-4 (DN4) questionnaire was used for the assessment of neuropathic pain.[10]

C. Furthermore, the Ewing score was calculated by summing the Cardiac Autonomic Reflex Tests (CARTs), which included the heart rate response to the deep breathing test, the immediate heart rate response to standing, and the blood pressure responses to standing and sustained handgrip testing.[29,30]

The patients were evaluated for their quality of life using the Arabic version of the Diabetes Quality of Life questionnaire, "DQOL".[31]

Primary and Secondary Outcomes

The primary outcome is the change in glycemic parameters and biological markers (TNF-α, MDA, and neurotensin). The secondary outcome is the change in the MNSI, DN4, and Ewing scores.

Sample Size Calculation

The sample size calculation was based on previous studies that revealed the mean difference of the effect of ALA on FBG was −6.57 mg/dl[32] and the effect of roflumilast on the same outcome was −21.2 mg/dl.[18] In this context, to detect an effect size of 0.815 with 80% statistical power and a 5% margin of error, the sample size required for this study is 56 patients (28 per group). With an assumed attrition rate of 15%, the initial sample size is 64 individuals (n = 32 per group).

Statistical Method

We performed statistical analysis using Jamovi 2.3.28.0. The Shapiro–Wilk test was used to test data normality. Non-normally distributed variables were presented as medians and interquartile ranges (IQRs). We used the Chi-Square (χ^2) or Fisher's exact test for categorical variables. The Mann–Whitney *U*-test was used to compare differences between groups for continuous variables. Within-group comparisons of continuous variables were achieved through the Wilcoxon Signed-Rank Test, while the changes in categorical variables within groups were evaluated using the McNemar test. Spearman's rank correlation was applied to assess the correlation between variables. The significance threshold was established at $P \leq 0.05$. Per-protocol analysis was used to analyze the data obtained from the current study.

Results

Figure 1 illustrates the participant flow chart. Out of 90 patients with type 2 diabetes mellitus screened for eligibility, 26 were excluded (6 patients declined participation, and 20 did not meet the inclusion criteria). Therefore, the remaining 64 patients were randomized and assigned to one of two study groups: Group 1 (roflumilast group; n = 32) and Group 2 (alpha-lipoic acid group; n = 32). During the study period, 3 patients in the roflumilast group dropped out secondary to non-adherence (n=2) and the development of thyroid cancer (n=1), and 3 patients in the alpha-lipoic acid group also dropped out as a result of non-compliance. Therefore, the final analysis involved 58 patients in both groups, with 29 patients in each group.

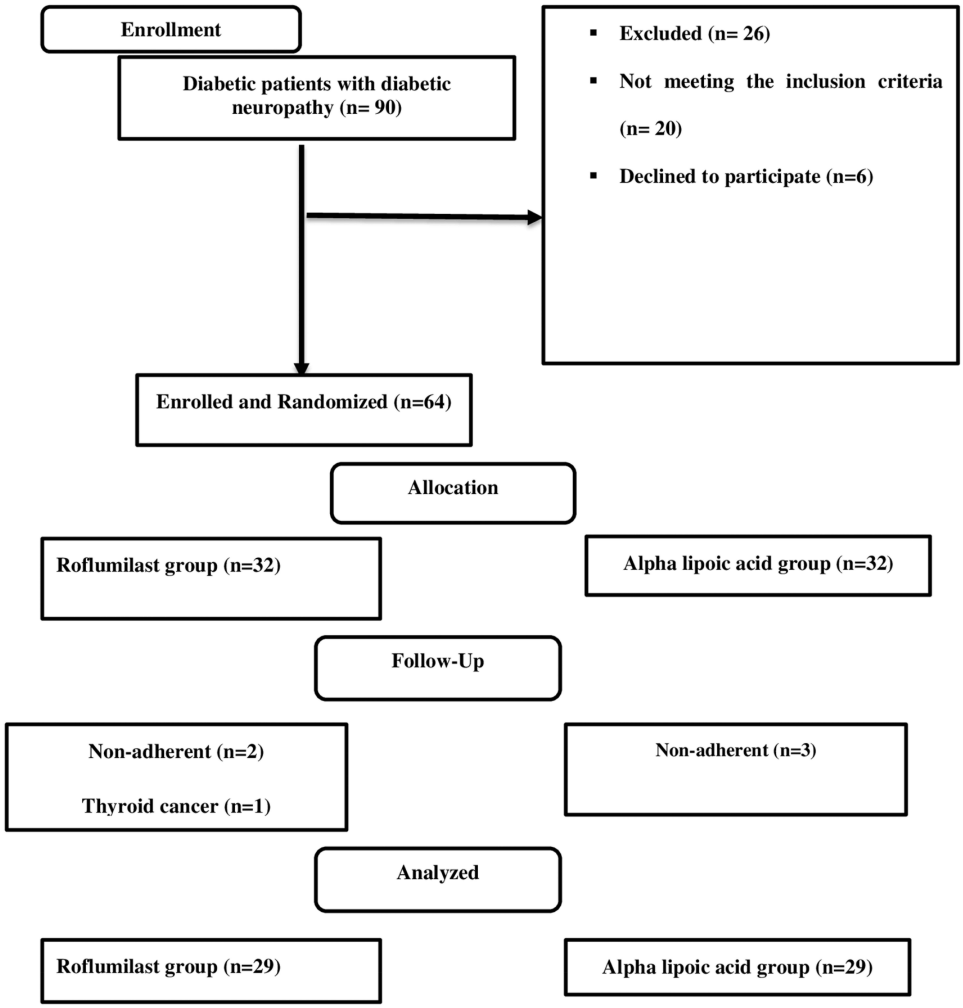

Figure 1 Participants flow chart.

Demographic, Clinical, and Laboratory Data

The baseline demographic, clinical, and laboratory data of the two study groups were not significantly different, as demonstrated in Table 1. There were no significant variations between the two study groups regarding age, sex ratio, weight, height, BMI, smoking status, family history of diabetes, duration of diabetes, hypertension, systolic and diastolic blood pressure ($P > 0.05$). In addition, the two groups were statistically similar regarding baseline laboratory parameters, including SCr, eGFR, vitamin B12 level, and ALT level ($P>0.05$) as postulated in Table 1.

Table 1 Baseline Characteristics for the Two Study Groups

Variables	Roflumilast (n=29)	Alpha-Lipoic Acid (n=29)	P-value
Age (years)	49 (10)	53 (12)	0.256
Sex			1
Female	22.0 (75.9%)	22.0 (75.9%)	
Male	7.0 (24.1%)	7.0 (24.1%)	

(*Continued*)

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Table 1 (Continued).

Variables	Roflumilast (n=29)	Alpha-Lipoic Acid (n=29)	P-value
Weight (kg)	79 (15)	80 (14)	0.369
Height (cm)	163 (7)	164 (5)	0.467
BMI (kg/m^2)	29.4 (6.83)	29.3 (5.12)	0.592
Smoking status No Yes	 25.0 (86.2%) 4.0 (13.8%)	 25.0 (86.2%) 4.0 (13.8%)	1
Family history of Diabetes No Yes	 12.0 (41.4%) 17.0 (58.6%)	 12.0 (41.4%) 17.0 (58.6%)	1
Duration of diabetes (years)	5 (2)	6 (2)	0.500
Duration of use of vildagliptin/metformin before running the study (months)	7 (1)	6 (2)	0. 081
Hypertension No Yes	 17.0 (58.6%) 12.0 (41.4%)	 16.0 (55.2%) 13.0 (44.8%)	0.791
SBP (mmHg)	120(0)	121(20)	0.422
DBP (mmHg)	83(10)	82(5)	0.410
SCr (mg/dl)	0.880 (0.240)	0.910 (0.220)	0.315
GFR (mL/min)	92 (25)	87 (26)	0.774
Vitamin B12 (pg/mL)	655 (241)	600(260)	0.981
ALT (U/L)	19.5 (5.60)	21.5 (7)	0.596

Notes: Qualitative data are presented as numbers and percentages. Quantitative data are presented as medians and interquartile ranges (IQR). P value <0.05 was considered significant.

Abbreviations: eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SCr, serum creatinine; Alt, alanine transaminase; Kg/m^2, kilogram per square meter; mmHg, millimeters of mercury; mg/dl, milligrams per deciliter; mL/min, milliliters per minute; pg/mL, picograms per milliliter; U/L, Units Per Liter.

Effect of Interventions on Glycemic and Biological Markers

At baseline, both groups were statistically similar regarding glycemic parameters and biological markers (P>0.05) as postulated in Table 2.

In the roflumilast group, HbA1c significantly decreased from a baseline median of 8.00% (IQR 0.80) to 7.30% (IQR 0.50) after 12 weeks (P1 < 0.001). Similarly, in the alpha-lipoic acid group, HbA1c declined from 8.00% (IQR 0.40) to 7.70% (IQR 0.50) (P1<0.001). Roflumilast treatment reduced FBG from 140 (17) to 118 (11) (P1<0.001), while alpha-lipoic acid reduced FBG from 139 (12) to 123 (10) (P1<0.001). In the roflumilast group, fasting insulin level was

Table 2 Glycemic Parameters and Biological Markers for the Two Study Groups Before and After Intervention

Variables	Roflumilast (n=29)			Alpha-Lipoic Acid (n=29)			P_2- value
	Baseline	Week 12	P_1-value	Baseline	Week 12	P_1-value	
HbA1C (%)	8 (0.800)	7.30 (0.5)	<0.001*	8 (0.400)	7.70 (0.500)	<0.001*	0.981 <0.001*
FBG (mg/dl)	140 (17)	118 (11)	<0.001*	139 (12)	123 (10)	<0.001*	0.913 <0.001*

(*Continued*)

Table 2 (Continued).

Variables	Roflumilast (n=29)			Alpha-Lipoic Acid (n=29)			P_2- value
	Baseline	Week 12	P_1-value	Baseline	Week 12	P_1-value	
Insulin (mU/L)	12.56 (2.590)	8.90 (2.925)	<0.001*	12.87 (2.455)	10.55 (2.18)	<0.001*	0.963 0.012*
HOMA-IR	4.33 (0.646)	2.69 (0.889)	<0.001*	4.29 (0.529)	3.28 (0.526)	<0.001*	0.643 <0.001*
HOMA-1β	58.7 (23.2)	58.3 (27.4)	<0.001*	60.9 (21.5)	59.5 (23.5)	<0.001*	0.734 0.914
TNF-α (ng/L)	15.5 (2.24)	11.8 (2.96)	<0.001*	17.3 (5.11)	12.6 (5.96)	<0.001*	0.076 0.132
MDA (nmol/L)	2.16 (0.970)	1.36 (0.461)	<0.001*	2.23 (1.200)	1.67 (0.558)	<0.001*	0.239 0.003*
NT (pmol/L)	10.64 (3.651)	7.99 (3.836)	<0.001*	12.02 (2.282)	8.76 (2.860)	<0.001*	0.100 0.626

Notes: Data are presented as medians and interquartile ranges (IQR). P-value <0.05 is considered significant. P_1-value: difference within the same group (before versus after treatment). P_2-value: difference between the two groups. * Statistically significant difference.
Abbreviations: HbA1C: glycated hemoglobin, FBG: fasting blood glucose, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance. HOMA-1 β: Homeostatic Model Assessment of Beta Cells, TNF-α: tumor necrosis factor alpha, MDA: malondialdehyde, NT: neurotensin, mg/dl: milligrams per deciliter, mU/L: milliunits per liter, ng/L: nanograms per liter, nanomoles per liter, pmol/L: picomoles per liter.

decreased from 12.56 (2.59) to 8.90 (2.925) (P1<0.001). On the other hand, the alpha-lipoic acid group also showed a reduction in fasting insulin level from 12.87 (2.455) to 10.55 (2.18) (P1<0.001). Roflumilast decreased HOMA-IR from 4.33 (0.646) to 2.69 (0.889) (P1<0.001), whereas alpha-lipoic acid reduced it from 4.29 (0.529) to 3.28 (0.526) (P1 < 0.001). The HOMA-1β was 58.7 (23.2) at baseline and 58.3 (27.4) at week 12 (P1<0.001) for the roflumilast group, while it was 60.9 (21.5) at baseline versus 59.5 (23.5) at week 12 (P1<0.001) for alpha-lipoic acid, as shown in Table 2.

Roflumilast reduced TNF-α serum level from 15.5 (2.24) to 11.8 (2.96) (P1<0.001), and alpha-lipoic acid decreased it from 17.3 (5.11) to 12.6 (5.96) (P1<0.001). In the roflumilast group, MDA serum level was decreased from 2.16 (0.97) to 1.36 (0.461) (P1<0.001), while in the alpha-lipoic acid group, MDA serum level was declined from 2.23 (1.20) to 1.67 (0.558) (P1<0.001). Roflumilast reduced neurotensin serum level from 10.64 (3.651) to 7.99 (3.836) (P1<0.001), and alpha-lipoic acid reduced neurotensin serum level from 12.02 (2.282) to 8.76 (2.86) (P1< 0.001), as shown in Table 2.

The comparison between the two study groups post-treatment indicated that the roflumilast group showed a significant decrease in HbA1C by 0.7% (8.8% relative reduction) compared to 0.3% (3.8% relative reduction) in the ALA group (P2< 0.001), FBG (P_2<0.001), fasting insulin level (P_2=0.012), and HOMA-IR (P_2<0.001). Similarly, serum MDA level was declined by 0.80 nmol/mL (37.0% reduction) with roflumilast versus 0.56 nmol/mL (25.1% reduction) with ALA (P2=0.003). However, the comparison of the two study groups post-intervention revealed the absence of significant variations between the two groups regarding serum TNF-α (P2=0.132), serum neurotensin level (P2=0.626), and HOMA-1β (P2=0.914) as postulated in Table 2 and Figure 2.

During the current study, we found that roflumilast achieved a significantly larger treatment effect on glycemic parameters compared to ALA. This superiority is confirmed by the very large between-group effect size (Cohen's d = −1.35, −1.10, and 1.30) for HbA1c, FBG, and HOMA IR, meaning that roflumilast provides a clinically meaningful difference in the metabolic outcome, as shown in Table 3.

During the current study, the 12-week administration of roflumilast led to a significant improvement in serum levels of TNF-α, MDA, and neurotensin compared to baseline data. The administration of roflumilast resulted in significant within-group reductions for TNF-α (Δ=−3.76 ng/L, d=−1.643), MDA (Δ=−0.813 nmol/mL, d=−1.382), and Neurotensin (Δ=−2.966 pmol/L, d=−1.058), all representing large within-group effects. This confirms the potent anti-inflammatory

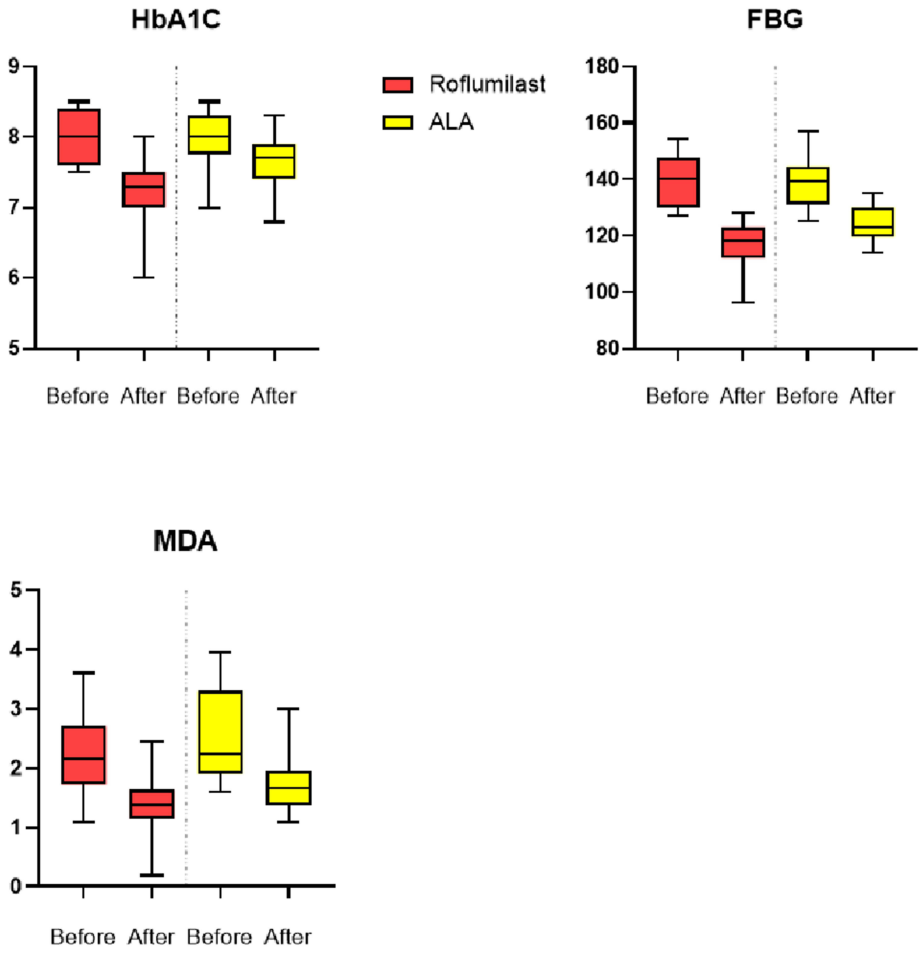

Figure 2 The comparison of HbA1C, FBG, and MDA between roflumilast and ALA before and 12 weeks post-intervention.

action of roflumilast. However, when comparing the two drugs, the between-group analysis for MDA showed a very small effect (d=−0.12; Hedges' g=−0.12, 95% CI: −0.63, 0.40), which indicates no meaningful difference between roflumilast and ALA as demonstrated in Table 3.

Table 3 The Median Absolute Change (Δ Abs) and the Approximate Between-Group Cohen's d (Change) for Glycemic, Biologic Parameters, and Neuropathic Scores

Outcome	Roflumilast Δ (abs)	Roflumilast %Δ	ALA Δ (abs)	ALA % Δ	Between-Group Cohen d (Change)	Hedges' g [95% CI]	Between-Group P2
HbA1c (%)	−0.70	−8.75%	−0.30	−3.75%	−1.35	−1.33 (−1.90, −0.76)	<0.001*
FBG (mg/dL)	−22	−15.71%	−16	−11.51%	−1.10	−1.08 (−1.64, −0.53)	<0.001*
Insulin (mU/L)	−3.66	−29.14%	−2.32	−18.03%	−0.70	−0.68 (−1.22,−0.14)	0.012*
HOMA-IR	−1.64	−37.88%	−1.01	−23.54%	−1.30	−0.68 (−1.22,−0.14)	<0.001*

(*Continued*)

Table 3 (Continued).

Outcome	Roflumilast Δ (abs)	Roflumilast %Δ	ALA Δ (abs)	ALA % Δ	Between-Group Cohen d (Change)	Hedges' g [95% CI]	Between-Group P2
HOMA-1β	−0.40	−0.68%	−1.40	−2.30%	0.45	0.44 (−0.10,0.98)	0.914
TNF-α (ng/L)	−3.70	−23.87%	−4.70	−27.17%	0.15	0.14 (−0.40,0.68)	0.132
MDA (nmol/L)	−0.80	−37.04%	−0.56	−25.11%	−0.12	−0.12 (−0.63, 0.40)	0.003*
Neurotensin (pmol/L)	−2.65	−24.91%	−3.26	−27.12%	0.05	0.05 (−0.49,0.59)	0.626
MNSIQ	−4.0	−50.0%	−4.0	−50.0%	0.00	0.00 (−0.54,0.54)	0.704
MNSIE	−1.5	−50.0%	−1.0	−33.3%	−0.15	−0.15 (−0.69,0.39)	0.705
DN4	−2.0	−66.7%	−1.0	−33.3%	−0.35	−0.34 (−0.88,0.20)	0.470

Notes: * Statistically significant difference.
Abbreviations: Δ, Change; HbA1c, Glycated hemoglobin; FBG, Fasting blood glucose; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HOMA-β:, Homeostatic Model Assessment of β-Cell Function; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; MNSIQ, Michigan Neuropathy Screening Instrument Questionnaire; MNSIE, Michigan Neuropathy Screening Instrument Examination; DN4, Douleur Neuropathique-4 questionnaire.

Clinical Assessment: Effect of Interventions on Diabetic Neuropathy

Both groups were statistically similar at baseline regarding MNSIQ, MNSIE, DN4, and Ewing scores ($P > 0.05$) as postulated in Table 4.

Table 4 Assessment of Diabetic Neuropathy and Quality of Life for the Two Study Groups

Variables	Roflumilast (n=29)			Alpha-Lipoic Acid (n=29)			P_2-value
	Baseline	Week 12	P_1-value	Baseline	Week 12	P_1-value	
MNSIQ	8 (1)	4 (3)	<0.001*	8 (2)	4 (3)	<0.001*	0.628 0.704
MNSIE	3 (0)	1.50 (1)	<0.001*	3(1)	2 (1)	<0.001*	0.317 0.705
DN4 Score	3 (1)	1 (1)	<0.001*	3 (2)	2 (1)	<0.001*	0.081 0.470
HR response to deep breathing	9 (3)	10 (4)	0.071	9 (2)	10 (7)	0.309	0.092 0.327
HR response to standing (30:15 ratio)	1 (0.04)	1.02 (0.0510)	0.173	1.01 (0.057)	1.01 (0.0425)	0.540	0.595 0.689
BP response to standing	10 (0)	10 (1)	0.284	10 (1)	10 (1)	0.909	0.076 0.721
BP response to handgrip testing	10(7)	10(7)	0.678	10 (1)	10 (1)	0.167	0.915 0.054

(*Continued*)

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Table 4 (Continued).

Variables	Roflumilast (n=29)			Alpha-Lipoic Acid (n=29)			P_2-value
	Baseline	Week 12	P_1-value	Baseline	Week 12	P_1-value	
Ewing score	2.5 (1)	2 (1)	0.119	2 (0.5)	2 (0.75)	0.879	0.381 0.257
DQL on satisfaction	45 (12)	47 (7)	0.009	45 (9)	44 (9)	0.004*	0.454 0.123
DQL on impact	34 (6)	28 (7)	<0.001*	32 (8)	28 (7)	<0.001*	0.253 0.925
DQL on worries	16 (2)	10 (2)	0.004*	14 (3)	12 (5)	0.013*	0.205 0.705

Notes: Data are presented as median and interquartile range (IQR). P-value <0.05 is considered significant. P_1-value: difference within the same group (before versus after treatment). P_2-value: difference between the two groups. * Statistically significant difference.
Abbreviations: MNSIQ, Michigan Neuropathy Screening Instrument Questionnaire; MNSIE, Michigan Neuropathy Screening Instrument Examination; DN4, Douleur Neuropathique en 4 Questions-Interview; DQL, stands for Diabetes Quality of Life.

The roflumilast group demonstrated a significant reduction in MNSIQ from 8 (1) at baseline to 4 (3) at week 12 (P1 < 0.001). Similarly, the alpha-lipoic acid group improved MNSIQ from 8 (2) to 4 (3) (P1<0.001). In the roflumilast group, the MNSIE score decreased from 3 (0) to 1.5 (1) (P1<0.001), whereas in the alpha-lipoic acid group, the MNSIE score was improved from 3 (1) to 2 (1) (P1<0.001). Roflumilast treatment reduced DN4 from 3 (1) to 1 (1) (P1<0.001), while alpha-lipoic acid reduced it from 3 (2) to 2 (1) (P1<0.001). However, twelve weeks after treatment, the CART measurements indicated that the scores for heart rate (HR) response to deep breathing and standing, and blood pressure response to standing and hand grip testing showed non-significant variations as compared to baseline values for both study groups (P>0.05), as shown in Table 4.

The comparison between the two study groups after treatment revealed non-significant variations between them regarding MNSIQ, MNSIE, DN4, and Ewing scores (P>0.05), as postulated in Table 4

Effect of Interventions on Diabetes Quality of Life

At baseline, both groups were statistically similar in diabetes quality of life (DQL) regarding satisfaction, impact, and worries (P >0.05) as presented in Table 4.

Roflumilast increased the satisfaction score from 45 (12) to 47 (7) (*P1* = 0.009), whereas alpha-lipoic acid decreased the satisfaction score from 45 (9) to 44 (9) (*P1* = 0.004). Roflumilast significantly reduced the impact score from 34 (6) to 28 (7) (*P1* < 0.001). Alpha-lipoic acid showed a similar improvement in impact score from 32 (8) to 28 (7) (*P1* < 0.001). In the roflumilast group, worries decreased from 16 (2) to 10 (2) (*P1* = 0.004). In the alpha-lipoic acid group, worry score was improved from 14 (3) to 12 (5) (*P1* = 0.013). However, the comparison between the two groups did not show significant variation in DQL scores for satisfaction, impact, and worries, as demonstrated in Table 4.

Correlation Between the Assessed Parameters

The pooled correlation analysis revealed a negative and significant correlation between both FBG and HbA1C, with MNSIQ (r = −0.597, r = −0.516, P <0.001), MNSIE (r = −0.686, r = −0.533, P<0.001), and DN4 (r = −0.576, r = −0.413, P<0.001). Fasting insulin levels and HOMA IR exhibited significant positive relationships with MNSIQ (r = −0.446, r =−0.618; P < 0.001), MNSIE (r = −0.434,r =−0.648; P < 0.001), and DN4 (r =−0.495, r = −0.638, P<0.001). Also, a significant negative correlation was established between inflammatory and oxidative markers, TNF-α and MDA, and MNSIQ (r = −0.439, r = −0.465; P<0.001), MNSIE (r =−0.345, r = −0.422, P<0.001), and DN4 (r =−0.261, r =−0.424, P<0.001). Additionally, a significant negative correlation was observed between NT and MNSIQ (r = −0.314; P < 0.001), MNSIE (r =−0.388, P<0.001), and DN4 (r =−0.418, P<0.001), as shown in Table 5.

Table 5 Correlation Between Biological and Clinical Variables

	MNSIQ	MNSIE	DN4
FBG	r=−0.597 (P<0.001)*	r=−0.686 (P<0.001)*	r=−0.576 (P<0.001)*
HbA1C	r=−0.516 (P<0.001)*	r=−0.533 (P<0.001)*	r=−0.413 (P<0.001)*
HOMA-IR	r=−0.618 (P<0.001)*	r=−0.648 (P<0.001)*	r=−0.638 (P<0.001)*
TNF-α	r=−0.439 (P<0.001)*	r=−0.345 (P<0.001)*	r=−0.261 (P=0.005)*
MDA	r=−0.465 (P<0.001)*	r=−0.422 (P<0.001)*	r=−0.424 (P<0.001)*
NT	r=−0.314 (P<0.001)*	r=−0.388 (P<0.001)*	r=−0.418 (P<0.001)*
Insulin	r=−0.446 (P<0.001)*	r= −0.434 (P<0.001)*	r= −0.495 (P<0.001)*

Notes: Spearman correlation was used to correlate non-parametric variables. P-value <0.05 is considered significant. * Statistically significant difference.

Abbreviations: r, Correlation coefficient; MNSIQ, Michigan Neuropathy Screening Instrument Questionnaire; MNSIE, Michigan Neuropathy Screening Instrument Examination; DN4, Douleur Neuropathique-4 questionnaire; FBG, fasting blood glucose; HbA1C, glycated haemoglobin; HOMA IR, homeostatic model assessment of insulin resistance; TNF-α, tumor necrosis factor-α; MDA, malondialdehyde; NT, neurotensin.

Drug Safety and Tolerability

The analysis of data from the current investigation indicated no significant difference between the two groups for the reported side effects, as illustrated in Table 6.

Table 6 The Reported Side Effects for Both Study Groups

Side Effects	Roflumilast (n=29)	Alpha Lipoic Acid (n=29)	P-value
Abdominal pain			0.706
No	24.0 (82.8%)	26.0 (89.7%)	
Yes	4.0 (13.8%)	2.0 (6.9%)	
Nausea			0.670
No	25.0 (86.2%)	27.0 (93.1%)	
Yes	4.0 (13.8%)	2 (6.9%)	
Headache			0.611
No	26.0 (89.7%)	28.0 (96.6%)	
Yes	3.0 (10.3%)	1.0 (3.4%)	

(*Continued*)

Table 6 (Continued).

Side Effects	Roflumilast (n=29)	Alpha Lipoic Acid (n=29)	P-value
Diarrhea			0.120
No	25.0 (86.2%)	29.0 (100.0%)	
Yes	4.0 (13.8%)	0.0 (0.0%)	

Notes: Data are presented as numbers and percentages. Chi-Square (X^2) was used to compare categorical variables. P-value <0.05 is considered significant.

One patient in the roflumilast group was diagnosed with thyroid cancer. This case of thyroid cancer observed during the current study was not a drug-related problem, and such a patient was excluded from the study.

Discussion

This study aimed to evaluate the efficacy and safety of roflumilast compared to alpha-lipoic acid (ALA) in patients with type 2 diabetes (T2DM) and diabetic neuropathy. The dose of ALA used during the present study was 600 mg orally once daily, which was selected based on a previous study demonstrating that 600 mg of oral ALA was safe and effective in reducing neuropathic pain in patients with diabetes.[33] The dose of roflumilast implicated during this trial was 500 mcg orally once daily, which was chosen based on its maintenance dose in patients with chronic obstructive pulmonary disease (COPD).[34] A treatment period of 12 weeks was chosen for the current study based on the observed decrease in glycated hemoglobin (HbA1C) following 12 weeks of administration of 500 mcg of roflumilast.[18] Additionally, it has been reported that the total symptom score (TSS) and neuropathy symptoms and Change (NSC) score decreased after 12 weeks of treatment with ALA.[33] Other studies demonstrated a significant reduction in vibration perception threshold (VPT), Neuropathy Total Symptom Score 6 (NTSS-6), visual analogue scale(VAS), and Total Symptom Score(TSS) after 12 weeks of treatment with ALA.[14,35]

During the current study, we found that roflumilast achieved a significantly larger effect size on glycemic parameters compared to ALA, as shown in Table 6.

The pathogenic mechanism underlying T2DM is oxidative stress and inflammation that disrupt glucose metabolism. Additionally, PI3K is altered, resulting in insufficient insulin release to produce nitric oxide, which antagonizes oxidative stress.[36] To elucidate the mechanisms by which roflumilast can enhance insulin sensitivity, a previous study demonstrated that inhibition of PDE4 by roflumilast increased hepatic Protein Kinase A (PKA) activity, subsequently leading to cAMP response element-binding protein (CREB) phosphorylation and the elevated production of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). PGC-1α serves as a principal regulator of mitochondrial biogenesis, and its elevated expression resulted in increased mitochondrial DNA content and improved respiratory capacity in hepatic and adipose tissues. Producing mitochondrial biogenesis presumably enhanced energy expenditure in patients treated with roflumilast.[37] Another study revealed that roflumilast stimulates insulin secretion by increasing cAMP, which activates glucagon-like peptide 1 (GLP-1) receptors, thereby promoting insulin production.[18] Our finding is compatible with previous studies that revealed that roflumilast, administered to newly diagnosed T2DM patients for 12 weeks, significantly reduces HbA1c and FBG levels, as well as insulin area under the curve.[18] Furthermore, it has been demonstrated that treatment with roflumilast in patients with polycystic ovarian syndrome (PCOS) significantly improved HOMA IR. However, another study reported that roflumilast administration did not decrease insulin and FBG.[37,38] These conflicting results and the lack of positive effect on insulin and FBG in this previous study could be explained on the basis that this study centered on people with PCOS and was primarily aimed at assessing weight reduction. In addition, the implicated sample size was too small to detect the potential effect of roflumilast on insulin resistance and FBG.

During the current study, the 12-week administration of roflumilast led to a significant improvement in serum levels of TNF-α, MDA, and neurotensin compared to baseline data as demonstrated in Table 6.

Additionally, 12 weeks post-intervention, the roflumilast group demonstrated a significant decrease in serum MDA levels relative to the ALA group. Roflumilast inhibits the release of PDE-4B and PDE-4D subtypes that mitigate the inflammation and oxidative stress through stimulating sirtuin-1 (SIRT-1) and AMPK by targeting Peroxisome proliferator-activated receptor (PPAR) and PGC to decrease oxidative stress and hence reduce neurotensin, MNSI, and DN4.[39] A former research postulated that roflumilast ameliorated the isoprenaline-induced cardiac toxicity in rats by reducing MDA and TNF-α-induced inflammation and through the elevation of antioxidant defense mechanisms.[40]

During the current study, alpha-lipoic acid (ALA) significantly improved glycemic parameters compared to baseline data, which is consistent with previous research. An updated systematic review and meta-analysis revealed that ALA significantly reduced insulin levels and HOMA-IR.[41] Another former study by Derosa et al indicated that treatment with ALA in diabetic patients for 3 months decreased HbA1C, FBG, and HOMA-IR.[42] This favorable effect of alpha-lipoic acid (ALA) on glycemic parameters could be explained by its insulin mimetic effect that stimulates insulin release to activate PI3K and phosphorylate insulin receptor substrate-1 (IRS-1) and thus stimulates glucose uptake via glucose transporter type 4 (GLUT4) gate-opening cells.[22,41] Furthermore, our data indicated that the administration of alpha-lipoic acid led to a significant decrease in serum levels of TNF-α, MDA, and neurotensin relative to baseline measurements. The beneficial effects of ALA on TNF-α, MDA, and neurotensin have been previously studied on paclitaxel and doxorubicin-induced neuropathy.[7,32,42] The positive impact of ALA on TNF-α is related to the inhibition of NF-κB with subsequent reduction of inflammatory markers such as TNF-α.[43] The decrease in MDA blood levels from baseline to twelve weeks post-intervention is facilitated by ALA's capacity to produce antioxidants, including vitamin C, vitamin E, and the enzyme superoxide dismutase (SOD), which mitigate the generation of reactive oxygen species.[13]

Concerning diabetic neuropathy (DN), roflumilast and ALA exerted similar effects on diabetic neuropathy. Both drugs significantly reduced neurotensin (NT), MNSIE, MNSIQ, and DN4 compared to baseline data. Post-treatment, there was no notable significant difference between the two study groups concerning diabetic neuropathy-associated measures. One of the suggested mechanisms underlying diabetic neuropathy is the disruption of the insulin signaling pathway. Insulin activates the PI3K-protein kinase B (Akt) pathway to facilitate nerve repair and myelin growth. During T2DM and oxidative stress, the repair process is impaired, and nerves cannot detoxify reactive oxygen species (ROS), making microglia more sensitive to neuropathic pain.[44–46] Roflumilast inhibits the release of PDE-4B and PDE-4D subtypes, which mitigate inflammation and oxidative stress, and thereby can reduce neurotensin, MNSIE, MNSIQ, and DN4.[39] No prior research has directly examined the effects of roflumilast on diabetic neuropathy; however, previous investigations have indicated its potential neuroprotective properties in other situations. Other authors have reported that roflumilast alleviates microglial senescence and retinal inflammatory neurodegeneration following retinal ischemia-reperfusion injury by inhibiting the NLR family pyrin domain-containing 3 (NLRP3) inflammasome.[47] Another former study indicated that roflumilast therapy alleviates functional and structural alterations in the hippocampus of depressed adult Wistar rats, highlighting its neuro-protective properties.[48] Furthermore, it has been demonstrated that roflumilast mitigates neuronal damage caused by ischemic stroke through its ability to diminish oxidative stress and regulate the Inositol-Requiring Enzyme 1α (IRE1α)/TNF Receptor-Associated Factor 2 (TRAF2)/c-Jun N-terminal Kinase (JNK) pathway.[49] In addition, a previous study revealed that roflumilast alleviates rotenone-induced Parkinson's disease in rats by activating the PI3K/AKT signaling pathway, enhancing motor function, and protecting dopaminergic neurons from degeneration.[50] These data indicate that roflumilast possesses considerable promise for addressing many types of neurodegenerations, perhaps including diabetic neuropathy. On the other hand, our current findings concerning the effect of ALA on diabetic neuropathy are similar to previously reported findings, which indicate that ALA significantly reduced MNSI and DN4 scores in patients with diabetic neuropathy.[51,52]

During the current study, neither roflumilast nor ALA significantly impacted CARTs, suggesting that roflumilast and ALA may have limited effects on these cardiac activities. Our previous finding aligns with the finding reported by Didangelos et al, who noted that ALA failed to reduce cardiac autonomic neuropathy.[51] An initial study by Zhang et al revealed that roflumilast significantly reduces doxorubicin-induced cardiotoxicity through its anti-inflammatory and anti-senescence effects, which are facilitated by activating Sirtuin-1 (SIRT-1) in cardiomyocytes. This study highlights the protective effect of roflumilast on heart cells against toxic injury by reducing inflammation and cellular senescence.[53] Another study by Xu et al postulated that roflumilast ameliorated hyperglycemia and cardiac dysfunction in mice by

inhibiting phosphodiesterase-4D (PDE-4D) and subsequently elevating muscle-specific miRNA miR-1 levels in the heart. This study suggests that roflumilast can improve heart function in diabetic conditions by targeting biochemical pathways beyond glucose reduction.[54] The processes governing cardiac autonomic reflexes differ from those related to inflammation, cellular senescence, and diabetes-induced heart remodeling. Autonomic reflexes are primarily governed by the autonomic nervous system, which regulates heart rate, blood pressure, and other involuntary bodily functions. Additionally, it is essential to note that our methodology for detecting cardiac autonomic neuropathy was based solely on pulse oximetry, which may not accurately measure heart rate variability; however, it is a more precise indicator of autonomic function. The discrepancies between the current study and prior findings may be attributed to variability in the disease state and the nature of the study (the difference between clinical, animal, and in vitro studies).

During the current study, both drugs significantly improved the quality of life of the allocated populations as compared to their baseline data. Although there is no previous clinical studies have examined the impact of both medications on quality of life using the same questionnaire used in the current study, similar results were noticed in patients with fibrotic sarcoidosis treated with roflumilast[55] and in diabetic patients with neuropathy treated with ALA for 40 days.[56]

During the present study, we observed a significant negative correlation between HbA1C, FBG, and neuropathic scores. Hyperglycemia was reported to be the main driving element in the pathogenesis of DN, and decreasing HbA1C and FBG could improve the symptoms, which seems consistent with the findings obtained with the current study.[20] Moreover, a cross-sectional study showed that insulin resistance might play a role in the development of DN, which was demonstrated in our trial by a negative correlation of fasting insulin and HOMA-IR with neuropathy.[57] Research on inflammation and oxidative stress in type 2 diabetes reported a significant link between TNF-α, MDA, and MNSI, which supports our finding concerning the presence of a negative relationship between inflammatory and oxidative biomarkers (TNF-α and MDA) and MNSI.[58,59] There was a lack of human studies that examine the relation between neurotensin with both MNSI and DN4, and the only evidence was based on the preclinical studies revealed that neurotensin modulates neuropathic pain through its action on spinal pain pathways.[60]

The findings from the current clinical study revealed no notable and significant difference in reported adverse effects between the roflumilast and alpha-lipoic acid groups. The reported adverse effects for both groups were mild, controllable, and transient, appeared during the initial treatment period, and resolved over time as the patients became tolerant to the treatments. The most commonly reported adverse effects of roflumilast were gastrointestinal side effects, which align with previous studies reporting that roflumilast exhibits the same adverse effects on intestinal cells as glucagon-like peptide-1.[37,61] Additionally, gastrointestinal adverse effects were the most reported adverse effects of alpha-lipoic acid, which is consistent with the findings of other authors.[62] The overall data indicate that roflumilast and alpha-lipoic acid were safe and well-tolerated. It is worth mentioning that, after randomization and during the follow-up period, one patient in the roflumilast group developed thyroid cancer. This case of thyroid cancer was not a drug-related problem, and such a patient was dropped out of the study because he stopped roflumilast, and we also decided to exclude him from the study to avoid interference with the measured parameters, since thyroid cancer is a well-known condition that affects insulin resistance and glucose homeostasis[63]. The present study's strengths encompass its design as a randomized controlled parallel trial, the consistent use of the same brand of roflumilast and alpha-lipoic acid throughout the study period, and, to the best of the authors' knowledge, its distinction as the first clinical study investigating the efficacy of roflumilast compared to alpha-lipoic acid in type 2 diabetic patients with diabetic neuropathy.

Limitations

Nonetheless, the current study possesses shortcomings, notably its limited sample size, being a single-center, open-label study with short duration, which may limit the ability to generalize the results or detect the long-term effects of the study medications on neuropathy scores. We recommend using devices that measure neuropathy outcomes, such as nerve conduction velocity and neurothesiometer. However, we considered the study to be open-label because roflumilast and ALA were different in physical appearance. Roflumilast was formulated as small, round tablets, and ALA was formulated as oblong-shaped, large tablets, which makes blinding impractical. However, given that the primary outcomes were glycemic and biochemical parameters rather than subjective measures, the bias seems minimal.

Conclusion

This randomized controlled parallel study revealed the efficacy and safety of roflumilast in type 2 diabetic patients with diabetic neuropathy. The administration of roflumilast for 12 weeks was associated with a significant decline in the glycemic parameters and oxidative stress marker compared to alpha-lipoic acid. Both drugs resulted in improvements in serum neurotensin levels, neuropathic symptoms, and neuropathic pain, as measured by the Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ), Michigan Neuropathy Screening Instrument Examination (MNSIE), and Douleur Neuropathique-4 (DN4), with no significant difference between the two drugs. However, both drugs failed to mitigate cardiac autonomic neuropathy, which was measured by Cardiac autonomic reflex tests (CART) and Ewing scores. Given that ALA represents a well-known therapy for diabetic neuropathy, roflumilast may have the potential to alleviate neuropathic symptoms; however, it requires further validation.

Future Directions

Future research should include larger, multicenter randomized double blind trials with longer follow-up to detect clinical changes in diabetic neuropathy-related scores and parameters. We recommend using an objective neuropathy score to mitigate bias. Mechanistic studies with biomarkers of inflammation, oxidative stress, and pharmacological action of PDE4 are needed to correlate the biochemical action of roflumilast with neuropathy outcome. Also, we recommend future studies that include patients with a wide range of BMI and glycated hemoglobin.

Institutional Review Board Statement

The research followed the ethical principles outlined in the Declaration of Helsinki, established in 1964. The study was approved by the Research Ethics Committees of Tanta University (Approval Code: 35420/4/22) and Menoufia University (Approval Code: 6/2022INTM). The study was registered in ClinicalTrials.gov, and its ClinicalTrials.gov ID is (NCT05369793).

Abbreviations

ALA, alpha-lipoic acid; FBG, fasting blood glucose; HbA1C, glycated hemoglobin; TNF-α, tumor necrosis factor-α; MDA, malondialdehyde; NT, neurotensin; HOMA-1β, Homeostatic Model Assessment of Beta Cell Function; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; MNSIQ, Michigan Neuropathy Screening Instrument Questionnaire; MNSIE, Michigan Neuropathy Screening Instrument Examination; DN4, Douleur Neuropathique-4; T2DM, type 2 diabetes mellitus; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; AGE, advanced glycation end product; PKC, protein kinase C; DAG, diacylglycerol; TNFR1, TNF-α receptor 1; P38 MAPK, mitogen-activated protein kinase P38; DN, diabetic neuropathy; CAN, cardiac autonomic neuropathy; ROS, reactive oxygen species; DPN, diabetic peripheral neuropathy; GLA, γ-linolenic acid; COPD, chronic obstructive pulmonary disease; PDE-4, phosphodiesterase type-4 enzyme; NF-κB, nuclear factor kappa B; IRE-1, inositol-requiring enzyme 1; ADA, American Diabetes Association; BMI, body mass index; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; SCr, serum creatinine; ECL, electrochemiluminescence; MNSI, Michigan Neuropathy Screening Instrument; DSPN, distal symmetrical peripheral neuropathy; CARTs, cardiac autonomic reflex tests; QOL, quality of life; DQOL, Diabetes Quality of Life; IQRs, interquartile ranges; χ^2, chi-square; HR, heart rate; TSS, total symptom score; NSC, Neuropathy Symptoms and Change; PKA, protein kinase A; CREB, cAMP response element-binding protein; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; GLP-1, glucagon-like peptide 1; PCOS, polycystic ovarian syndrome; SIRT-1, sirtuin-1; PPAR, peroxisome proliferator-activated receptor; GLUT4, glucose transporter type 4; SOD, superoxide dismutase; NLRP3, NLR family pyrin domain-containing 3; IRE1α, inositol-requiring enzyme 1α; TRAF2, TNF receptor-associated factor 2; JNK, Jun N-terminal kinase; PDE-4D, phosphodiesterase-4D.

Data Sharing Statement

Data can be obtained upon reasonable request from the corresponding author.

Informed Consent Statement

All participants in this study provided informed consent before participating in the research.

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All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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