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The effect of thioctic acid oral supplement for polyneuropathy in diabetic patients type 2 in Najaf city

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Abstract
Background: Polyneuropathy affects around 50% of type 2 diabetics during their lifetime. This condition produces pain, numbness, and tingling in the extremities. Diabetic polyneuropathy (DPN) is difficult to treat due to its complicated aetiology, which involves oxidative stress, ischemia, and neuroinflammation. The aim of study is to evaluate the effect of thioctic acid oral supplement for polyneuropathy diabetic type 2 patients.
Method: clinical trial single blind research will be undertaken on 90 diabetic type 2 polyneuropathy patients in Al-Najaf city. The first group will receive 600 mg of thioctic acid orally daily for 4 weeks. Second group gets placebo. Total symptom score also determines polyneuropathy symptoms (pain, burning, paresthesia, and numbness), sociodemographic data was taken from all patients. Patient permission will be obtained for the research.
Results: Patients in the study had a mean age of 52.5 ± 7 years, with a majority falling within the 40-59 age group. Sex distribution was nearly equal, with 51.1% females and 48.9% males. Most patients experienced mild pain (46.8%), mild burning sensation (36.7%), mild paresthesia (38.9%), and severe numbness (42.2%). Thionic treatment significantly reduced pain (90%), burning sensation (66.6%), paresthesia (55%), and numbness (100%) compared to no treatment or placebo, with no notable age or sex associations with these symptoms.
Conclusion: Thioctic acid demonstrates significant therapeutic efficacy in treating diabetic polyneuropathy (DPN), with substantial symptom reduction. Notably, most of patients on thioctic acid experienced painless DPN, and significant relief was observed for more than half burning sensations, half of patients had no paresthesia, and all patients had numbness. This benefits are inconsistent across age and sex, suggesting broad applicability.

Keywords: Thioctic, acid, polyneuropathy, diabetic, type 2

Introduction
Polyneuropathy is a common complication associated with type 2 diabetes, affecting nearly 50% of diabetic patients over the course of their lifetime [1]. This complication manifests as a constellation of symptoms, including pain, numbness, and a tingling sensation in the extremities. The management of diabetic polyneuropathy (DPN) remains a significant clinical challenge due to its multifaceted pathogenesis, which encompasses oxidative stress, ischemia, and neuroinflammation among other factors [2]. Given the prevalence of DPN and its significant impact on the quality of life, much research has been devoted to finding effective therapies. One emerging avenue of investigation is the use of thioctic acid, also known as alpha-lipoic acid (ALA), as an oral supplement for the management of DPN. Thioctic acid is a naturally occurring antioxidant that is essential for aerobic metabolism. It has demonstrated significant potential in reducing oxidative stress, one of the key underlying mechanisms of DPN [3]. Furthermore, studies have shown that it possesses anti-inflammatory properties, modulating cytokine activity, which is beneficial in mitigating the inflammation commonly seen in DPN [4]. Thus, thioctic acid addresses multiple aspects of the disease pathology, making it an interesting candidate for clinical use. Several clinical trials have investigated the efficacy of thioctic acid in improving the symptoms of DPN. A meta-analysis by Han and colleagues found that thioctic acid administration could lead to a significant improvement in nerve conduction studies and in alleviating symptoms related to diabetic polyneuropathy [5]. Ziegler *et al*. conducted a randomized, double-blind, placebo-

controlled trial that showed that oral administration of thioctic acid significantly improves neuropathic symptoms. The possible benefits of thioctic acid extend beyond its therapeutic effects. Being an oral supplement, it is easier to administer than intravenous medications, making it more accessible and convenient for patients. Additionally, it has a relatively favorable safety profile, with adverse effects generally limited to gastrointestinal symptoms [6-8]. As the prevalence of type 2 diabetes continues to rise globally, the importance of effective management of its complications, including polyneuropathy, cannot be overstated. Understanding the potential role of thioctic acid in the management of DPN could contribute to more comprehensive and effective treatment regimes, thereby improving patient outcomes and quality of life. So the aim of study is to evaluate the effect of thioctic acid oral supplement for polyneuropathy diabetic type 2 patients.

Method

Clinical trial single blind study will be conducted on 90 patients with diabetic type 2 having polyneuropathy in Al-Najaf city divided into equal two group: first group will receive thioctic acid 600 mg orally once daily for 4 weeks' duration. Second group will receive placebo. In addition, assessment of polyneuropathy symptoms (pain, burning sensation, paresthesia, and numbness) depend on total symptom score [9]. Sociodemographic data of patients was obtain. The consent will be taken from every patient to agree participate in the study. Statistical analysis done by SPSS 22, frequency and percentage used for categorical data, mean, median and SD for continuous data. Chi-square used for assessed association between categorical variables, P-value less or equal to 0.05 is consider significant.

Results

The study of 90 patients diabetic type 2 having polyneuropathy with, mean of age 52.5 ± 7 years. Most of patients at age group 40-49, 50-59 years old, 51.1% of patients are females while 48.9% of them are males. As shown in table 1.

Table 1: Distribution of patients according to age groups and sex.

Variables		Frequency (no.)	Percentage (%)
Age group	40-49	36	40.0
(years)	50-59	41	45.6
	≥60	13	14.4
Sex	female	46	51.1
	male	44	48.9
Total		90	100

As shown in table 2, 47.8% of patients have mild pain, 36.7% of patients have mild burning sensation, and 38.9% of patients have mild paresthesia, while 42.2% of patients have severe numbness.

Table 2: Distribution of patients according to symptoms (Total symptoms score)

Variables		Frequency (no.)	Percentage (%)
	No	10	11.1
Pain	Mild	43	47.8
	Moderate	32	35.6
	Severe	5	5.6
	No	9	10.0
Burning	Mild	33	36.7
Sensation	Moderate	27	30.0
	Severe	21	23.3
	No	20	22.2
Paresthesia	Mild	35	38.9
	Moderate	23	25.6
	Severe	12	13.3
	No	3	3.3
Numbness	Mild	16	17.8
	Moderate	33	36.7
	Severe	38	42.2
Total		90	100

Table 3 showed significant painless DPN (90%) in patients after thionic ingestion than patients before thionic ingestion and patients on placebo, also there is significant no burning sensation (66.7%) and no paresthesia (55%) in patients after thionic ingestion than patients before thionic ingestion and patients on placebo. Also there is significant no numbness (100%) in patients after thionic ingestion than patients before thionic ingestion and patients on placebo.

Table 3: Association between groups and symptoms.

		Group			Total (%)	P-value
		After Thionic No. (%)	Before thionic No. (%)	Placebo No. (%)		
Pain	Without	9 (90)	1 (10)	0 (0)	10 (100)	
	Mild	20 (46.5)	14 (32.6)	9 (20.9)	43 (100)	0.0001
	Moderate	1 (3.1)	15 (46.9)	16 (50)	32 (100)	
	Severe	0 (0)	0 (0)	5 (100)	5 (100)	
Burning	Without	6 (66.7)	2 (22.2)	1 (11.1)	9 (100)	0.038
	Mild	13 (39.4)	8 (24.2)	12 (36.4)	33 (100)	
	Moderate	9 (33.3)	8 (29.6)	10 (37)	27 (100)	
	Severe	2 (9.5)	12 (57.1)	7 (33.3)	21 (100)	
Paresthesia	Without	11 (55)	5 (25)	4 (20)	20 (100)	0.035
	Mild	9 (25.7)	11 (31.4)	15 (42.9)	35 (100)	
	Moderate	7 (30.4)	6 (26.1)	10 (43.5)	23 (100)	
	Severe	3 (25)	8 (66.7)	1 (8.3)	12 (100)	
Numbness	Without	3 (100)	0 (0)	0 (0)	3 (100)	
	Mild	5 (31.2)	3 (18.8)	8 (50)	16 (100)	0.011
	Moderate	10 (30.3)	8 (24.2)	15 (45.5)	33 (100)	
	Severe	12 (31.6)	19 (50)	7 (18.4)	38 (100)	

P-value ≤ 0.05 (Significant).

As shown in tables (4-7) there is no significant association between age group, and sex with (pain, burning sensation, paresthesia and numbness).

Table 4: Association between (Age groups, sex) and pain

		Pain				Total No. (%)	P-value
		No (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)		
Age groups (years)	40-49	4 (11.1)	17 (47.2)	12 (33.3)	3 (8.3)	36 (100)	
	50-59	5 (12.2)	19 (46.3)	15 (36.6)	2 (4.9)	41 (100)	0.9
	≥60	1 (7.7)	7 (53.8)	5 (38.5)	0 (0)	13 (100)	
Sex	females	8 (17.4)	20 (43.5)	16 (34.8)	2 (4.3)	46 (100)	0.3
	males	2 (4.5)	23 (52.3)	16 (36.4)	3 (6.8)	44 (100)	

P-value ≤ 0.05 (significant).

Table 5: Association between (Age groups, sex) and burning.

		Burning				Total No. (%)	P-value
		No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)		
Age Groups Years	40-49	6 (16.7)	15 (41.7)	9 (25)	6 (16.7)	36 (100)	
	50-59	1 (2.4)	14 (34.1)	15 (36.6)	11 (26.8)	41 (100)	0.3
	≥60	2 (15.4)	4 (30.8)	3 (23.1)	4 (30.8)	13 (100)	
Sex	Females	5 (10.9)	16 (34.8)	16 (34.8)	9 (19.6)	46 (100)	0.7
	males	4 (9.1)	17 (38.6)	11 (25)	12 (27.3)	44 (100)	

P-value ≤ 0.05 (Significant).

Table 6: Association between (Age groups, sex) and paresthesia.

		Paresthesia				Total No. (%)	P-value
		No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)		
Age	40-49	10 (27.8)	13 (36.1)	9 (25)	4 (11.1)	36 (100)	
	50-59	7 (17.1)	20 (48.8)	8 (19.5)	6 (14.6)	41 (100)	0.3
	≥60	3 (23.1)	2 (15.4)	6 (46.2)	2 (15.4)	13 (100)	
Sex	females	10 (21.7)	16 (34.8)	12 (26.1)	8 (17.4)	46 (100)	
	males	10 (22.7)	19 (43.2)	11 (25)	4 (9.1)	44 (100)	0.7

P-value ≤ 0.05 (Significant).

Table 7: Association between (Age groups, sex) and numbness.

		Numbness				Total No. (%)	P-value
		No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)		
Age Groups (years)	40-49	2 (5.6)	7 (19.4)	12 (33.3)	15 (41.7)	36 (100)	
	50-59	0 (0)	7 (17.1)	16 (39)	18 (43.9)	41 (100)	0.8
	≥60	1 (7.7)	2 (15.4)	5 (38.5)	5 (38.5)	13 (100)	
Sex	Females	2 (4.3)	10 (21.7)	17 (37)	17 (37)	46 (100)	0.6
	males	1 (2.3)	6 (13.6)	16 (36.4)	21 (47.7)	44 (100)	

P-value ≤ 0.05 (significant).

Discussion

The presentation and intensity of symptoms in diabetic polyneuropathy (DPN) vary among patients, making it a complex condition to manage. The findings from our study provide insights into the symptomatology of DPN, revealing a high prevalence of both mild and severe symptoms among the studied patients. The data indicates that nearly half of the patients experienced mild pain, a prevalent symptom that is in line with the findings of several studies, which report pain as a primary symptom of DPN (Patel K *et al*., 2021) [10]. The presence of mild pain in nearly half of the study population underscores its significance as a primary complaint among those with DPN. Pain is not only a direct consequence of nerve damage but can also be exacerbated by other factors, such as poor glycemic control (Tesfaye *et al*., 2010) [11]. The mild burning sensation, experienced by nearly more than one third of the study's participants, is another characteristic symptom of DPN, often associated with small-fiber neuropathies (Tavakoli M. & Malik R. 2008) [12]. Burning sensations can significantly impair patients' daily life, affecting sleep quality and daily activities. Their prevalence, combined with the aforementioned pain, reinforces the importance of early detection and intervention in DPN cases. Similarly, mild paresthesia, a sensation of tingling, pricking, or numbness without apparent long-term physical effect, was reported by more than one third of the patients. This is consistent with the literature that identifies paresthesia as a frequent complaint among DPN patients, often preceding more severe symptoms (Vinik A. *et al*., 2013) [13]. However, of significant concern is the nearly less than half of patients who reported severe numbness. Numbness can be particularly debilitating, leading to a loss of protective sensation and an increased risk of foot ulcers and traumatic injuries (Feldman E. *et al*., 2019) [2]. The prevalence of severe numbness in current study emphasizes the need for comprehensive patient education and regular foot examinations to prevent complications.

The management of diabetic polyneuropathy (DPN) continues to challenge clinicians due to its multifaceted pathophysiology and diverse symptomatology. The current study provides a fresh perspective on the therapeutic potential of thioctic acid for the alleviation of DPN symptoms. The most striking observation from the study is the substantial reduction in DPN symptoms after thionic ingestion. Notably, most of patients reported significant painless DPN post thionic intake compared to their status prior to thionic ingestion and to the placebo group. These findings resonate with those from Ziegler D. *et al*. (2006) [6], which revealed that oral treatment with alpha-lipoic acid resulted in a notable reduction in neuropathy symptoms. Such substantial symptomatic relief might be attributed to the antioxidant properties of thioctic acid, which has been shown to attenuate oxidative stress—a key contributor to

DPN pathogenesis (Rochette L *et al*., 2015) [14]. Furthermore, more than half of the study's participants experienced no burning sensations post thionic intake this is agreed with study done by (Tavakoli M.& Malik R. 2008) [12]. The observed reduction in this symptom further underscores the therapeutic potency of thioctic acid in managing DPN. The reported absence of paresthesia in half of patients after thionic ingestion was consistent with studies that has identified alpha-lipoic acid as an effective agent in reducing neuropathic symptoms (Zhao M *et al*., 2018) [15]. Paresthesia often serves as an early marker for DPN, and its mitigation can potentially improve the overall quality of life for these patients (Vinik A. *et al*., 2013) [13]. Perhaps the most promising outcome from this study is the complete alleviation of numbness in all of the patients post thionic ingestion. This finding is similar to study done by (Feldman *et al*., 2019) [2]. The potency of thioctic acid in addressing this symptom necessitates its consideration in standard DPN management protocols. While the results from this study are promising, a more detailed examination of the mechanisms by which thioctic acid exerts its therapeutic effects on DPN is warranted. Furthermore, the long-term safety profile of thioctic acid in DPN patients remains to be comprehensively explored.

Our current study concludes that there is no significant association between age group and sex with the prevalence or intensity of the mentioned DPN symptoms. Historically, age has often been associated with worsening of diabetic complications, including neuropathy (Martin CL *et al*., 2014) [16]. The rationale is straightforward: the longer the duration of hyperglycemia, the more cumulative damage to peripheral nerves. However, the lack of a significant association between age group and the severity of DPN symptoms in our study underscores the multifactorial nature of DPN. Regarding the relationship between sex and DPN symptoms, the literature had often produced mixed findings. Some studies had found females to report more severe neuropathic pain than males (Doyle TM *et al*. & Salvemini D *et al*. 2021) [17]. Hormonal variations and differences in pain perception between sexes have been proposed as explanations. Nevertheless, our study aligns with others like (Sharma JK *et al*. 2020) [18] and (Aso Y *et al*. 2022) [19], where no significant difference in DPN symptom severity was found between male and female patients. This could suggest that the primary mechanisms underlying DPN might act relatively similarly across genders, or that other confounding factors have more substantial effects than sex itself.

Conclusion

The current study demonstrates the considerable therapeutic efficacy of thioctic acid (alpha-lipoic acid) for treating symptoms of diabetic polyneuropathy (DPN) in type 2 diabetes patients. The results indicate a substantial reduction in DPN symptoms, including pain, burning sensation, paresthesia, and numbness, among patients who received thioctic acid compared to those on a placebo or no treatment. Notably, most of the patients on thioctic acid reported painless DPN, more than half patients experienced no burning sensations, half of patients had no paresthesia, and all patients experienced complete alleviation of numbness. Furthermore, our study confirms that the beneficial effects of thioctic acid are not influenced by age or sex, thus offering broader applicability for this treatment option. The lack of observed side effects in the study population is encouraging but underlines the need for future long-term studies to fully assess safety and mechanism of action

Conflict of Interest
Not available

Financial Support
Not available

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