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Review Article

Role of N-Acetyl Cysteine in the Management of Diabetic Peripheral Neuropathy: A Systematic Review

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ABSTRACT

The most prevalent and costly diabetes-related consequence is diabetic neuropathy, with multiple therapies that failed to improve painful symptoms. An anti-oxidant and glutathione inducer, N-acetyl cysteine (NAC) has been utilized as a mucolytic in individuals with specific lung problems and as an antidote for acetaminophen overdose. It also emerges as a promising treatment for diabetic peripheral neuropathy (DPN). This review aimed to assess the effect of acetylcysteine on DPN. To identify relevant studies, Google Scholar, PubMed, Science Direct, Egyptian Knowledge Bank (EKB), and clinical trial.gov were systematically searched. Pre-defined search terms were used; "NAC as an anti-oxidant", "NAC treatment", "acetylcysteine treatment and DPN"," Diabetic Peripheral Neuropathy", "NAC in Neuropathic pain". Only English-based trials that are in full text were included. Seven studies were evaluated for NAC treatment effects in DPN. Randomized controlled trials and pre-clinical animal studies were the main interest of the review while pre-clinical studies including cell lines were excluded. In conclusion, most of the studies showed promising results in improving either the assessed scores or the biomarkers. Since most of the conducted studies were animal-based studies, future clinical randomized controlled studies are essential to confirm the results.

Keywords: *Acetylcysteine; Diabetic neuropathy; in vivo studies; interventional studies; clinical trials.*

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1. Introduction

Diabetic neuropathy which is mostly caused by a somatosensory nerve system lesion is one of the clinical conditions known for its severe morbidity and pain **[1]**. Approximately 50% of people with diabetes acquire diabetic peripheral neuropathy (DPN), which is the most prevalent and expensive diabetes-related complication **[2]**.

There are numerous pathophysiological pathways **(Fig. 1)**, including different metabolic and intracellular signaling systems, via which diabetes results in neuropathic damage. These mechanisms are still not fully understood. In nerve biopsies from both animal models and clinical trials with diabetic polyneuropathy, axonal degradation with primary and secondary demyelination has been observed **[3]**.

It has been demonstrated that the myelin sheath and Schwann cells are specifically impaired. Both myelinated and unmyelinated neurons experience dissociation from axons. As a

result, there is a disruption in axonal impulse conduction and signaling along with a decrease in neurotrophic factors. This leads to a progressive loss of distal axons and centripetal degeneration that varies in length regarding its progression **[4]**.

This suggests that the longest nerve fibers-such as the sciatic and sural nerves-are the most susceptible to being involved **[5]**.

One of the suggested mechanisms appears to be the induction of nerve injury via cellular and metabolic pathways by an inflammatory process. Also, there appears to be a correlation between metabolic risk factors related to diabetes and diabetic peripheral neuropathy **[3]**.

It has been demonstrated that obesity and type 2 diabetes, or both together, may be linked to an elevated inflammatory response. Individuals diagnosed with type 2 diabetes were shown to have higher serum concentrations of inflammatory biomarkers, such as C-reactive protein (CRP), interleukin (IL) 6, or IL 18 **[6]**.

Previously, Herder and co-workers discovered that systemic biomarkers of inflammation were likewise connected to the emergence and progression of neuropathy over 6.5 years of monitoring in an elderly population with diabetes in a prospective clinical trial **[7]**.

Moreover, Oxidative stress is a result of macrophage activation linked to peripheral nerve inflammation **[7]**. The development of diabetic peripheral neuropathy has also been linked to increased amounts of reactive oxygen species, particularly mitochondrial overproduction of superoxide. Clinical research on diabetic patients with or without neuropathy has revealed a poor total antioxidant status in comparison to healthy people, as well as an increase in the oxidative stress index and total oxidative status **[6]**. Prior research has shown that patients with newly diagnosed type 1 and type 2 diabetes exhibit signs of systemic oxidative stress even in the presence of good glycemic control. These findings have also suggested a role for poor superoxide extracellular defense in the early development of diabetes mellitus **[8]**.

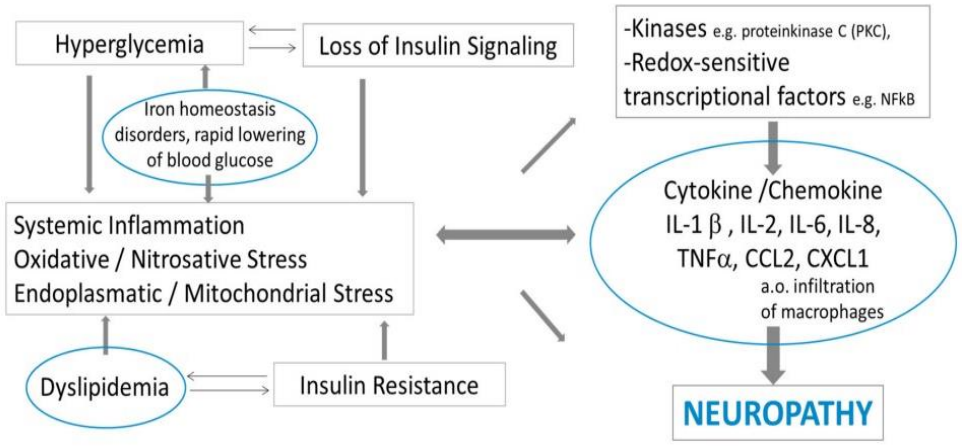

Fig. 1. Pathophysiology of diabetic peripheral neuropathy. Peripheral nerve fiber injury and inflammation are related to each other in diabetes: hyperglycemia and insulin loss or resistance cause dyslipidemia and oxidative/nitrosative stress in the mitochondria and endoplasmic reticulum. These mechanisms could be involved in the formation of reactive oxygen species (ROS), inflammation, and cellular damage. The peripheral nerves' infiltrating macrophages cause the production of pro-inflammatory substances such as chemokines and cytokines, which worsen inflammation and cause damage to the nerve fibers. Iron homeostasis abnormalities and abrupt blood glucose drops exacerbate peripheral nerve inflammation **[6]**.

Burning, numbness, tingling, pain, and/or weakness that start in the distal lower limbs and escalate into more severe neuropathic pain symptoms are prevalent symptoms in about 10–30% of affected individuals **[9]**. The debilitating symptoms can be intermittent or persistent, and for many, they result in depression, sleep disturbances, and a general decline in quality of life **[10]**.

Damage to sensory neurons may worsen pre-existing diabetic foot ulcers, with DPN being the strongest beginning risk factor for neuropathic ulcers. Because of the limb numbness that follows, ulcers go unnoticed for longer lengths of time, as a result, neither counsel nor remedial measures are sought in the early phases of the disease **[2]**.

Foot problems and amputations can be decreased by up to 85% by raising awareness of diabetic foot issues, performing risk assessments, and having a multidisciplinary team taking care of the feet **[11]** Fifty to seventy percent of nontraumatic amputations are associated with diabetic neuropathy. For this reason, it's critical to identify risk factors and diabetic neuropathy symptoms as soon as possible to establish interventions and stop additional neuronal damage **[12]**.

The main risk factor for diabetic neuropathy is hyperglycemia. In type 1 diabetes, better glycemic management can stop the disease's progression towards diabetic neuropathy; however, it cannot stop type 2 diabetes distal polyneuropathy from developing **[12]**.

A significant risk factor for neuropathy is the duration of diabetes, and it is commonly known that age and diabetes duration both raise the chance of getting neuropathy. Since nerve damage from hyperglycemia takes time, diabetic neuropathy is more prevalent in elderly persons (over 50 years) **[13]**.

Despite having appropriate glucose control, patients with type 2 diabetes experience distal symmetric polyneuropathy. Multiple comorbidities, including obesity, dyslipidemia, and hypertension, may have lessened the positive effects of glucose control. Cardiovascular risk factors, such as low high-density lipoprotein, hypertriglyceridemia, abdominal obesity, hypertension, and dyslipidemia, can exacerbate diabetic neuropathy without affecting glycemic control **[14]**.

DPN is not easily prevented or treated, and it can be challenging for both the patient and the treating physician. Glycemic management has a beneficial effect on preventing DPN in people with type 1 diabetes, but numerous clinical trials have not demonstrated a comparable benefit for patients with type 2 diabetes **[13]**.

In addition to glycemic management, the American diabetic association guidelines for managing DPN suggest diet and exercise as essential treatment measures for people with type 2 diabetes and DPN. Glycemic management is therefore probably significant for type 2 diabetes patients, although further therapies are required and recommended as standard of care **[15]**.

DPN lacks effective pharmaceutical treatments; nevertheless, sodium-glucose cotransporter (SGLT)-2 inhibitors offer a new approach, particularly to a greater extent in the context of type 1 diabetes **[16]**; however, human studies are still lacking **[17]**.

As there are currently no proven disease-modifying treatments, patient education regarding DPN, the value of regular shoe care, yearly foot examinations, and excellent foot hygiene are the main goals of clinical management for DPN patients **[14]**.

Pain control is another crucial aspect of DPN management. For painful DPN, four pharmacological classes—sodium channel

blockers, gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors-work well. The impact size of all these drugs is comparable, and variations within a class are probably negligible or nonexistent. Consequently, considerations such as cost, tolerability, and other contraindications should be given equal weight when selecting a neuropathic painkiller, in addition to efficacy. There are topical medicines as well, the most researched being capsaicin **[18]**.

Capsaicin has effects that are similar to those of oral medications. All of these drugs have modest overall effects, and only around 1 in 7 patients with painful DPN report feeling less pain **[19]**, highlighting the obvious need for more potent pain management strategies **[17]**.

Moreover, behavioral therapies are available to alleviate excruciating DPN. Research on mindfulness, cognitive behavioral therapy, and exercise has shown early promise **[20]**.

When treating painful DPN that is not alleviated by a single modality, combination therapy- which combines behavioral therapy, pharmacological, or topical medications-may be necessary **[17]**.

There are also surgical options for the treatment of excruciating DPN. Regretfully, it's still unclear how spinal cord stimulation works **[21]**.

Opioids, such as tapentadol and tramadol, efficiently alleviate pain in DPN patients when used for a short period, While their long-term usefulness is unknown. Furthermore, long-term opioid use can have serious negative effects, including dependence, overdose, and death, and painful DPN is chronic **[22]** hence these medications should be avoided in this population **[17]**.

While many physicians prescribe tapentadol or tramadol as substitutes for other opioids, new research indicates that they may have similar detrimental long-term effects. Guidelines for great caution when treating with opioids for persistent non-cancer pain have been developed as a result of this evidence **[18, 23]**.

To create a more effective treatment for DPN with fewer side effects, drug repurposing can be a very compelling strategy as an alternative to researching and developing new pharmacological compounds. A different approach to handling any safety issues is drug repurposing. The goal of drug repurposing research is to identify novel, previously unknown effects of licensed medications used in clinical practice trials. Reducing the duration and expense of drug development can be achieved by employing approved medications that have undergone prior human pharmacokinetic and safety profile testing. As a result, drug repurposing should be taken into account and applied promptly to patients suffering from DPN **[24-26]**.

The role of oxidative stress in DPN has been intensively studied. Oxidative stress resulting from an imbalance between cellular antioxidant levels and oxidant levels has been implicated in causing cell damage and increasing the risk of diabetic complications **[1]**.

The accumulation of free radicals and decreased activity of antioxidant enzymes in diabetic animals with diabetic neuropathy served as the primary evidence of oxidative stress involvement in the progression of the disease, and the effect was mitigated concurrently with symptom relief with antioxidant treatment **[1]**.

Long-term hyperglycemia in type 2 diabetes raises the risk of oxidative stress and an unbalanced concentration of oxygen and nitrogen free radicals, which creates a vicious cycle that releases reactive oxygen species (ROS) **[27]**.

Research has indicated that ROS are mostly produced by mitochondria and nicotinamide

adenine dinucleotide phosphate (NADPH) oxidase under hyperglycemic settings. This results in the creation of superoxide anion, which is primarily responsible for the difficulties associated with diabetes **[28]**.

Inflammation and the ROS that follow can both cause mitochondrial malfunction, which is linked to DPN **[1]**.

Consequently, antioxidants are thought to be one of the medicinal products used to treat diabetic neuropathy. Various antioxidants like Alpha-lipoic acid, vitamins A, C, and E, taurine, melatonin, and acetyl-L-carnitine have been studied with conflicting results to slow the progression of DPN **[1]**. Owing to the fact that ALA reduced diabetic neuropathy symptoms in clinical trials, it is believed to be a useful therapeutic option **[29, 30]**, While additional research is needed to determine the role of vitamins A, C, and E in diabetic neuropathy **[31]**.

NAC a glutathione precursor and cysteine prodrug is an old antioxidant with potential promising mechanisms **(Fig. 2)** that could address the problems encountered in DPN in both animal studies and clinical trials, NAC has been suggested as a possible treatment for many disorders, including diabetic neuropathy, whose pathophysiology involves oxidative stress **[32]**.

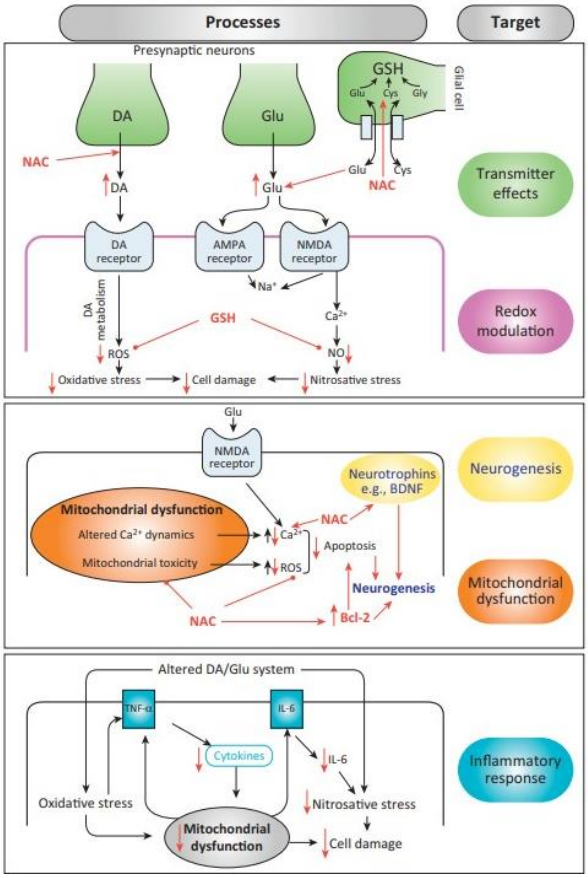

Fig. 2. Physiologic objectives of N-acetylcysteine (NAC) that have been proposed. The several ways that NAC functions as a neurotransmitter, regulates redox reactions, encourages neurogenesis, resolves mitochondrial dysfunction, and reduces inflammation **[49]**.

AMPA, 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; BDNF, brain-derived neurotrophic factor; Bcl-2, B cell lymphoma 2; Ca, calcium; Cys, cysteine; DA, dopamine; Glu, glutamate; Gly, glycine; GSH, glutathione; IL, interleukin; NAC, N-acetylcysteine; NMDA, Nmethyl-D-aspartate; NO, nitrous oxide; ROS, reactive oxygen species; TNF, tumor necrosis factor

NAC regulates other pathophysiologic processes linked to disease in addition to

oxidative stress. These include indirect effects on neurotransmitters including glutamate and dopamine as well as mitochondrial malfunction, apoptosis, and inflammation **[33]**.

Increasing intracellular cysteine will subsequently increase glutathione. Isolated uses of both GSH and cysteine were ineffective in raising GSH levels within cells. That's why NAC is one of the main methods for reducing the damage caused by oxidative stress in cases of xenobiotic intoxication, such as paracetamol, or pathologies related to GSH deficiency, through the maintenance of their levels in various tissues **[34]**.

Increasing intracellular glutathione, a key element of the mechanisms that protect cells from oxidative stress, will consequently slow the progression of DPN. Moreover, NAC has direct free radical scavenging activity via supplying sulfhydryl groups **[35]**.

The nuclear factor kappa B (NF-κB) and Nuclear Factor Erythroid 2-related Factor 2 (Nrf2) pathways are critical for preserving the equilibrium between antioxidants and oxidative stress, as well as for preventing tissue inflammation and cell death.Nrf2 controls the expression of several antioxidant genes and starts the transcription of downstream regulatory antioxidant proteins. It lowers cellular oxidative damage, participates in ROS detoxification and scavenging, and preserves the intracellular redox balance **[36]**.

A previous study revealed that NAC increased levels of Nrf2 by enhancing Nrf2 expression **[37]**.

Nuclear factor kappa B (NF-κB) plays an important role in the inflammatory cascade and immunological response involved in the reaction to oxidative stress. NF-κB transcription factor has the responsibility of controlling the expression of genes that promote inflammation. NAC inhibits NF-κB and blocks the translocation and nuclear activation of NF-κB transcription factor. Also, NAC has been shown to inhibit the release of inflammatory cytokines in lipopolysaccharide-activated macrophages, including Tumor necrosis factor alpha (TNFα), IL-1β, and IL-6 **[38]**.

NAC's anti-oxidant and anti-inflammatory properties may also be connected to its mitochondria-protective activities **[39]**. Furthermore, some recent studies showed that NAC can suppress mitochondrial membrane potential (MMPs) and limit nociceptive responses to provide analgesic effects in animal models of inflammatory and neuropathic pain **[40, 41]**.

Considering the multiple pathogenetic pathways associated with diabetic neuropathy, such as inflammation and oxidative stress, NAC may be a viable option for treating DPN.

2. Material and Methods

These systematic review findings were reported using the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines (http://www.prisma-statement.org).

2.1. Data sources and search strategy

A systemic search was conducted through three major electronic databases; Google Scholar (https://scholar.google.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Science Direct (https://sciencedirect.com/), and clinical trial.gov. (https://clinicaltrials.gov/). These electronic databases were accessed from the 15th of June to the 28th of July 2024. Clinical trials till July 2024 were analyzed. Search terms used were "acetylcysteine treatment in diabetic neuropathy", "NAC as an anti-oxidant", "NAC treatment", "acetylcysteine treatment and DPN"," Diabetic Peripheral Neuropathy" and "NAC in Neuropathic pain".

2.2. Study screening and selection

Original English-written full-text trials were

selected for inclusion in this review. Basic information such as the name of the main author, year of publication, study design, sample size, patient population, intervention, and control used, outcomes, and conclusions were reviewed for randomized control trials and observational studies used in this review.

2.3. Inclusion and Exclusion Criteria

The Preferred Reporting Items for Systematic Reviews (PRISMA) criteria were followed in the gathering of the data for this systematic review. This study did not require approval from an institutional review board since it used data that had already been published.

The inclusion criteria were as follows: (i) patients having diabetic neuropathy and (ii) patients received N-acetyl-cysteine medication regardless of formulation, dose, or route of delivery. Basic science, biochemical, and pre-clinical in vitro study designs were excluded. Finally, we also excluded any non-English studies.

3. Results

The flow chart of study selection is demonstrated in **Fig. 3**. A total of 16420 studies were found during the investigational scholarly search. We eliminated 600 duplicate studies, 1300 pre-clinical in vitro studies, 73 systematic review articles and meta-analyses, and 14,440 studies including NAC with other diseases. The remaining qualified full text were 7 studies that evaluated the effect of NAC treatment in DPN.

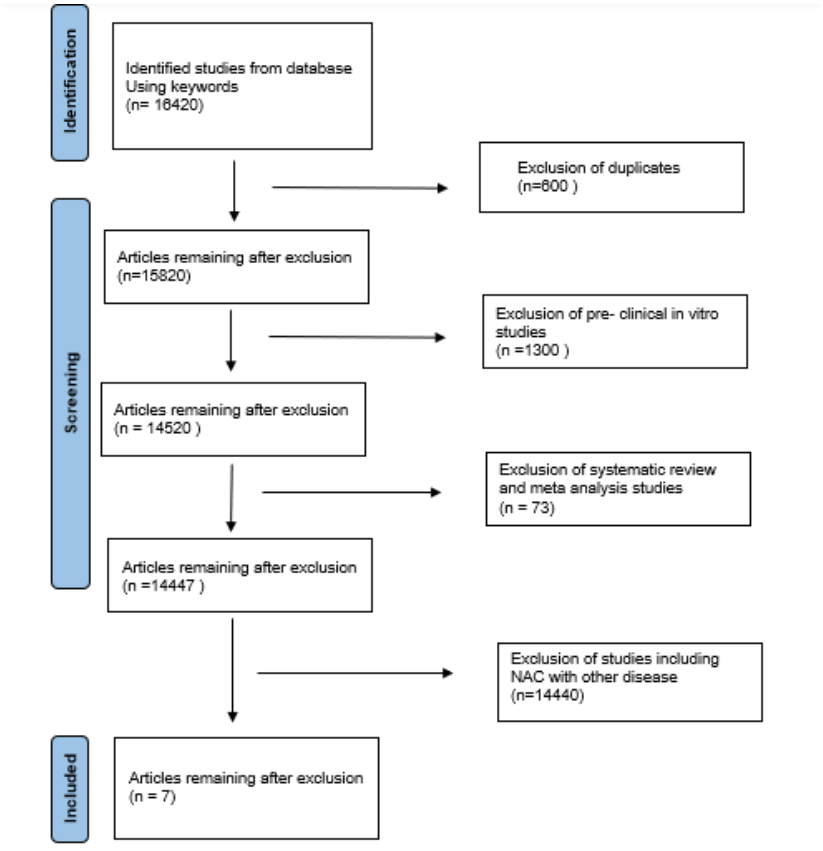

Fig. 3. The flow chart of the study

3.1. Overview of included studies

An overview of the included studies in this review based on trial design and study population is presented in **Table 1**.

Table 1. An overview of the included studies in this review based on trial design and study population

Trial	Population/ species	Objectives	Intervention (Methods/overview)	Results/Outcome
Sagara et al.1996 [42]	Diabetic Wistar rats	A study aimed to examine whether NAC inhibits peripheral neuropathy	For a period of 12 to 15 weeks, Wistar rats that were 12 weeks old, weighing roughly 250 g, and 6 weeks old weighing roughly 230 g, were used for functional and biochemical studies while a period of 22 weeks for functional and structural studies.	NAC did not affect blood glucose levels or the nerve glucose, sorbitol, and cyclic adenosine monophosphate contents, whereas it corrected the decreased glutathione levels in erythrocytes, the increased lipid peroxide levels in plasma & the increased lipopolysaccharide-induced tumor necrosis factor alpha activity in sera of diabetic rats. NAC inhibited the development of functional & structural abnormalities of peripheral nerve in streptozotocin-induced diabetic rats.
Kamboj et al.2010 [43]	Rats were used	The main aim of the study was to evaluate the extent to which NAC inhibited oxidative stress and apoptotic indicators that were caused by hyperglycemia in diabetic neuropathy.	Diabetic rats were given NAC with a dose between 1.4 and 1.5 g/kg/day for 7 weeks.	The anatomical abnormalities in diabetic rats' sciatic nerve were reversed with NAC. Findings indicate that NAC has a protective effect that is mediated by reducing oxidative stress and apoptosis. Highlighting NAC's potential as a treatment for diabetic neuropathy.
Horst et al. (2014) [44]	Adult male Wistar Rats were used	Examining the effect of NAC on the spinal cord glutathione system in rats with neuropathic pain	Three experimental groups were established for Rats (24 rats per group), and each was further divided into 4 subgroups (6 rats in each subgroup), which received NAC for 3 or 10 days, at a dose of 150 mg/kg/day or 0.9% saline solution, Intraperitoneally.	GPx activity increased later due to NAC.
Notartomaso et al. (2020) [45]	Mice were used	Analyzing NAC's impact in a rat model with excruciating diabetic neuropathy.	Groups of 6-7 mice were treated intraperitoneally daily for 7 days with saline or NAC (25–100mg/kg).	NAC relieved pain associated with diabetic neuropathy & showed promise as an adjuvant drug in diabetic patients.
Li et al. (2021) [46]	Rats were used	The study aimed to evaluate NAC's potential therapeutic effect in Rats having DPN.	Rats were randomly divided into 3 groups of 6 rats per group: control group (C), untreated diabetic rats group (D), & diabetic rats group treated with NAC (D+N). NAC dose of 1.5 g/kg/day was used.	NAC treatment could effectively alleviate DPN

Heidari et al. 2019 [47]	T2DM patients having DPN	Study aimed to investigate the effectiveness of oral (NAC), as an adjuvant therapy in patients suffering from DPN.	A total of 113 patients with eligibility criteria having T2DM suffering from DPN were randomly allocated to either the pregabalin and placebo or pregabalin and NAC group for 2 months (pregabalin with dose 150 mg/day, NAC and matched placebo with doses 600 mg two times/ day).	Serum level of MDA was markedly decreased while serum levels of superoxide dismutase, GPx, TAC, and TTG were markedly increased by adjuvant NAC.
Sajedi et al.2024 [48]	Type 2 diabetic patients having PDN	The study aimed to investigate the effects of oral NAC versus pregabalin in DPN.	102 eligible patients with T2DM & DPN were allocated at random into two groups, pregabalin (150 mg/day) or NAC (600 mg/ twice a day) for 2 months.	Serum levels of MDA and NO were markedly decreased by NAC, while an increase in TAC, TTG, and catalase activity was detected, on the other side, Pregabalin markedly lowered serum levels of MDA, and NO but elevated TAC.

4. Discussion

The effect of NAC and its possible beneficial effects for DPN, when added to diabetes treatment plans, is being explored. An in vivo study by Horst et al addressed the effect of NAC on the spinal cord glutathione system in rats with neuropathic pain where a late increase in glutathione peroxidase levels by NAC was achieved **[44]**. Also, using a mouse model of painful diabetic neuropathy, Notartomaso et al evaluated the analgesic effect of NAC. The results showed that NAC produced a robust analgesic effect in diabetic mice both following a single injection and subsequent injections, indicating that NAC is a safe medication with a favorable pharmacokinetic profile that may be used in conjunction with traditional analgesics to treat painful diabetic neuropathy **[45]**.

Owing to NAC's role on oxidative stress and Inflammatory mediators, Li et al conducted a study aimed at evaluating the possible therapeutic effect of the antioxidant NAC in rats having DPN showing that treatment with NAC decreased the Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) protein expression, NAC also significantly reduced or reversed the increases in plasma Interleukin-6, TNF-α, superoxide dismutase -1, superoxide dismutase-2, malondialdehyde (MDA), and 15-F2t-Isoprostane in rats having diabetes. Hence, It was proven that NAC therapy could successfully reduce DPN. **[46]**.

One of the main factors causing diabetic neuropathy is oxidative stress. Due to the autoxidation of monosaccharides, chronic hyperglycemia causes oxidative stress and the subsequent generation of hydroxyl and superoxide radicals. It is generally recognized that the generation of reactive oxygen species is necessary for the transmission of pain. Kamboj et al in their study assessing the NAC effect in inhibiting hyperglycemia-induced oxidative stress and apoptosis markers in diabetic neuropathy resulted in a significant decrease in glutathione peroxidase (GPx) activity in sciatic nerve as relative to the control animals after two months of diabetes. However, treatment with NAC restored GPx activity. The study concludes that the administration of NAC therapy reduces thermal hyperalgesia caused by hyperglycemia and diminishes the oxidative stress-induced apoptosis that may be the cause of diabetes-related nerve damage. The results imply that treating persistent diabetics having neuropathy using NAC may be effective **[43]**. Lastly, in terms of in vivo research, Sagara et al.'s study

found that giving diabetic rats NAC treatment both morphologically and electrophysiologically inhibited the onset of peripheral neuropathy. These effects could be mediated by NAC's several actions, which include increasing glutathione levels intracellularly, shielding cells from free radical damage, and preventing the overproduction of tumor necrosis factor **[42]**.

Only two double-blinded clinical trials evaluate the efficacy of NAC as an adjuvant therapy to alleviate painful diabetic neuropathy clinical symptoms.

Heidari et al revealed in their study, using NAC moderate doses of 600 mg two times per day for two months, a decrease in mean pain score and mean sleep interference score when comparing NAC added on pregabalin versus the control group taking pregabalin only. Significant improvement in patient global impression of change (PGIC) and clinical global impression of change (CGIC) from baseline to the end of the study was reported in the patients taking pregabalin and NAC. According to their research, practically all patients tolerated oral NAC well and experienced few side effects. Furthermore, regarding oxidative stress biomarkers, adjuvant NAC markedly decreased serum levels of MDA and elevated serum levels of superoxide dismutase, glutathione peroxidase, total antioxidant capacity (TAC), and total thiol groups (TTG). One of their study limitations was using a moderate dose, suggesting using higher doses in the upcoming studies **[47]**.On the other hand, Sajedi et al in their study comparing NAC 600 mg two times per day for two months versus Pregabalin, stated that the decline in mean pain score and elevation in sleep interference score (SIS) was similar between both groups. More improvement in PGIC and CGIC from the baseline was found in the NAC group. NAC, markedly, lowered serum levels of MDA, and Nitric oxide (NO), but elevated TAC, TTG, and catalase activity (CAT) while Pregabalin, markedly, lowered serum levels of MDA, and NO but elevated TAC. Concluding that NAC is effective in alleviating DPN symptoms which is probably attributed to its antioxidant effects **[48]**.

Conclusion

Although most of the studies evaluating the effect of NAC in improving symptoms of DPN are in vivo, they elaborated on the effect of NAC from different aspects, markers, and scores. More clinical trials are needed to be conducted with a longer follow-up period, different doses of NAC, and different markers and scores to further confirm the therapeutic effectiveness of NAC as an antioxidant and anti-inflammatory agent.

List of abbreviations

NAC, N-acetyl cysteine; DPN, Diabetic peripheral neuropathy; EKB, Egyptian Knowledge Bank; CRP, C-Reactive protein; IL, Interleukin; NF-κB, Nuclear factor kappa B; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; SGLT, Sodium-glucose cotransporter; ROS, Reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; GPx, Glutathione peroxidase; MDA, Malondialdehyde; TAC, Total antioxidant capacity; TTG, Total thiol groups; NO, Nitric oxide; TNF-α, Tumor necrosis factor-alpha; PGIC, Patient global impression of change; CGIC, Clinical global impression of change; SIS, Sleep interference score; CAT, Catalase activity.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Availability of data and material

Data will be made available on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Sherien Mohamed Emara, Sarah Farid Fahmy, Mona Mohamed Abdel Salam, and Lamia Mohamed El-Wakeel. The first draft of the manuscript was written by Sherien Mohamed Emara and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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