

## Potential Positive Effects using Coenzyme Q10 Supplement as Adjuvant Therapy to Gabapentin for Managing Diabetic Neuropathy

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### Abstract

The most prevalent chronic complication of diabetes mellitus is diabetic neuropathy. The pathogenesis of diabetic neuropathy is exacerbated by hyperglycemia-induced oxidative stress, which causes nerves to deteriorate in a programmed manner. Many clinical trials depend on supplement in an attempt to improve neuropathy symptoms such as (pain & tingling) and patient quality of life, one of them is Coenzyme Q10 which is reported to have an anti-inflammatory and antioxidant effects, and was totally nontoxic and non-reported side effects. This study aimed to evaluate using a Coenzyme Q10 supplement as an adjuvant therapy to gabapentin to improve the clinical symptoms of diabetic neuropathy in relation to its anti-inflammatory and antioxidant effects. This open-label interventional study involved 33 diabetic neuropathy patients divided into two groups: group (1) 16 patients were given 300 mg of gabapentin once a day at evening, plus group (2) 17 patients received 300 mg of gabapentin once a day in the evening plus Coenzyme Q10 200mg once daily. Pre- and post-3 months of treatment, blood samples used to measure metabolic, anti-inflammatory and antioxidant biomarkers (fasting blood glucose, glycated hemoglobin, tumor necrosis factor- $\alpha$ , Interleukin-6 & Superoxide dismutase), as well as the Michigan neuropathy screening instrument for assessment of clinical symptoms. After 3 months of Coenzyme Q10 use, the results showed that the group 2 produced a highly significant change in glycated hemoglobin & fasting blood glucose levels. Meanwhile, there is no significant change in glycated hemoglobin & fasting blood glucose values in patients receiving just gabapentin. Moreover, results showed highly significant differences in Michigan neuropathy screening instrument, tumor necrosis factor- $\alpha$ , interleukin-6 & superoxide dismutase between the study groups at the completion of the research. Finally, addition of Coenzyme Q10 to gabapentin for diabetic neuropathy patients result in improving the glycemic control & symptoms of the diabetic neuropathy, as well as decreasing effects of the inflammation in addition to oxidative stress after three months of treatment.

**Keywords:** Diabetic neuropathy, Coenzyme Q10, Gabapentin, Neuropathy symptoms.

### التأثيرات المحتملة المضادة للالتهابات والمضادة للأكسدة لمكمل الإنزيم المساعد CoQ10 كعلاج مساعد للكابابنتين

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### الخلاصة:

اعتلال الأعصاب السكري هو أكثر المضاعفات المزمنة شيوعاً لمرض السكري. يؤدي الإجهاد التأكسدي الناتج عن ارتفاع السكر في الدم إلى موت الخلايا المبرمج للأعصاب، مما يساهم في أمراض الاعتلال العصبي السكري. تعتمد العديد من التجارب السريرية على المكملات في محاولة لتحسين أعراض الاعتلال العصبي مثل (الألم والوخز) ونوعية حياة المريض، أحدها هو الإنزيم المساعد CoQ10 والذي ورد أن له تأثيرات مضادة للالتهابات ومضادة للأكسدة، وتماماً ليس لديه أي تأثير سام وخالي من الآثار الجانبية. تهدف هذه الدراسة إلى تقييم استخدام CoQ10 كعلاج مساعد لجابابنتين لتحسين الأعراض السريرية لاعتلال الأعصاب السكري وعلاقتها بتأثير الدواء المضاد للالتهابات والمضاد للأكسدة. شملت هذه الدراسة التداخلية المعروفة التسمية 33 مريضاً يعانون من اعتلال الأعصاب السكري تم تقسيمهم إلى مجموعتين. المجموعة (1) 16 مريضاً تناولوا جابابنتين 300 مجم مرة واحدة يومياً في الليل، والمجموعة (2) 17 مريضاً تناولوا جابابنتين 300 مجم مرة واحدة يومياً في الليل بالإضافة إلى CoQ10 200 مجم مرة واحدة يومياً. قبل وبعد 3 أشهر من العلاج، استخدمت عينات ومصل الدم لقياس مؤشرات التمثيل الغذائي ومضادات الالتهاب ومضادات الأكسدة (TNF- $\alpha$  و HbA1c و FBG) و IL-6 و SOD)، بالإضافة إلى اختبار ميشيغان (MNSI) لتقييم شدة أعراض السريرية. بعد 3 أشهر من استخدام Co Q10 أظهرت النتائج أن مجموعة 2 أنتجت تغيراً مهماً للغاية في مستويات HbA1c و FBG بعد 3 أشهر من مكملات Co Q10 وفي الوقت نفسه، لا يوجد تغيير كبير في مستويات HbA1c و FBG في المرضى الذين عولجوا باستخدام جابابنتين لوحده. علاوة على ذلك، أظهرت النتائج تأثير ذات دلالة معنوية عالية في MNSI و TNF- $\alpha$  و IL-6 و SOD بين مجموعات الدراسة في نهاية الدراسة. أخيراً، إضافة مكمل CoQ10 إلى الجابابنتين في مرضى الاعتلال العصبي السكري يؤدي إلى تحسين السيطرة على نسبة السكر في الدم وأعراض الاعتلال العصبي السكري، بالإضافة إلى تقليل تأثير الالتهاب والإجهاد التأكسدي بعد ثلاثة أشهر من العلاج.

الكلمات المفتاحية: اعتلال الأعصاب السكري، الجابابنتين، أعراض الاعتلال العصبي، CoQ10.

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## Introduction

Diabetes mellitus (DM) would be a collection of metabolic disorders marked by the irregular metabolism of carbohydrate, fat, and protein; as a result to impaired insulin secretion or insulin action <sup>(1)</sup>. According to the International Diabetes Federation (IDF), there were roughly 425 million persons living with diabetes globally in 2017, with the number expected to rise to 629 million by 2045. <sup>(2)</sup> Long-lasting hyperglycemia results in multi systemic problems of the eyes, nerves, kidneys, heart, and blood vessels. As a result of macro- and micro-vessel disorders, diabetes causes high rates of morbidity and mortality <sup>(3)</sup>.

Diabetic neuropathy, also known as peripheral nerve damage, is one of the most prevalent comorbidities of diabetes <sup>(4)</sup>. It leads to an increased risk for significant functional limits and dangerous consequences, such as amputation of the legs <sup>(5)</sup>. The pathologic process of diabetic neuropathy is characterized by three major changes: first, nuclear factor kappa B, activator protein 1, and mitogen-activated protein kinases are mostly activated by inflammation. Second, Polyol, hexosamine, protein kinase C, advanced glycosylation end-products, and glycolysis all seem to be involved in oxidative stress caused by hyperglycemia. Third, the majority of reactive oxygen species are produced by mitochondrial malfunction. Lipid peroxidation, protein modification, and nucleic acid damage are all caused by free radicals, which leads to axonal degeneration and segmental demyelination <sup>(6)</sup>.

Several treatments have been assessed to minimize neuropathic deficits and enhance nerve function, which including oral anti diabetics, statins, anti-inflammatory, antioxidants, anticonvulsant, and other medications approved for neuropathy <sup>(7)</sup>.

CoQ10 is an endogenously produced molecule that serves as an electron carrier in the mitochondrial respiratory chain. CoQ10 would be an anti-oxidant that scavenges free radicals and inhibits lipid peroxidation, in addition to its particular role in the mitochondria <sup>(8)</sup>. CoQ10 is shown to have therapeutic value in the treatment of diabetes and its related complications <sup>(9)</sup>. Serum CoQ10 levels in patients with diabetes are frequently low, which may be linked to subclinical diabetic cardiomyopathy that can be reversed with CoQ10 treatment <sup>(10)</sup>. CoQ10 therapy increased serum CoQ10 values, enhanced endothelial function within brachial artery, which significantly reduced systolic and diastolic blood pressures, in addition to glycosylated hemoglobin levels (HbA1C) <sup>(11)</sup>. CoQ10 enhanced diabetic polyneuropathy nerve conduction measures and lowered oxidative stress while having minimal side effects; it decreases serum glucose levels by improving  $\beta$ -cells functions in addition to insulin requirements were lowered due to greater insulin sensitivity for patients with diabetes <sup>(12)</sup>. These

findings suggest that CoQ10 could be used as a supplement to treat peripheral neuropathy in people with type 2 diabetes in the future.

## Patients and Methods

A prospective open-label randomized-controlled interventional trial designed to explore potential an anti-inflammatory & antioxidant effects of CO Q10 supplement as adjuvant therapy in diabetic neuropathy patients. The study was conducted from October 2017 to 31th July 2018. The study was performed on 40 Iraqi patients of both genders (male & female) diagnosed with type 2 diabetic with neuropathy. All patients have been selected from the national diabetes center for treatment and research/ Mustansiriya university, following approval of the scientific committee in the National Diabetes Center. Seven patients excluded from the study due to incompliance and missed treatment dose (Only 33 patients completed the study)

Patients were involved in the trial if they meet certain criteria: 1) Adult patient 18-70 years old. 2) Mild-moderate cases diabetic neuropathy. But the following were the exclusion criteria: 1) Pregnancy and breastfeeding. 2) Severe case diabetic neuropathy. 3) Patients with other comorbid diseases. 4) Patients hypersensitive to any drug or supplement used in this study. Over the course of 3 months, the employed patients were followed up on. They were divided into two groups based on the physician's treatment recommendations. (**Group 1**): involved 16 patients treated with the conventional gabapentin capsules 300 mg as single daily dose at night. (**Group 2**): included 17 patients treated with the conventional gabapentin capsules 300 mg as single daily dose at night plus Coenzyme Q10 capsules 200mg once daily for 3months.

Patient demographics, clinical symptoms, diabetes history, and diabetes test results (FBS, and HbA1c) have all been documented. Serum Interleukin 6 (IL6), TNF-alpha & SOD were measured using ELISA kits. Clinical tests were carried out to determine the severity of symptoms of the DN; Michigan Neuropathy Screening Instrument (MNSI) <sup>(13)</sup>. Furthermore, specific questionnaire was used to assess the intensity of clinical symptoms pre and post-treatment <sup>(14)</sup>. All patients were treated for 3 months, and blood samples were taken at the start of the trial (baseline values) and again three months later to assess any changes in the examined parameters.

## Ethical consideration

The scientific and ethical committee of Mustansiriya University- College of Pharmacy gave their approval to this study. The National Diabetes Center for Treatment and Research came to an agreement. Patient written agreement was

obtained after a thorough description of the study's purpose, ensuring the accuracy of the data collected.

#### Statistical analysis

The data were analyzed using the following software, Microsoft excel, Minitab v17, and SPSS V24. The results reported in this study were expressed as mean  $\pm$  SD. Chi square test, paired t-test to comparing variables before and after treatment in the same group. The one-way analysis of variance (ANOVA) was performed in order to determine and find differences among independent variables and to assess the degree of significance.

Probability values  $>$  (0.05) regarded not significant different, whereas P values  $<$  (0.05) were regarded significantly different, & P  $<$  (0.01) was considered highly significant different.

#### Results

The Table (1) summarizes the demographic information and baseline characteristics of the study participants. In this table, there were non-significant variations among patients allocated in each group regarding to age, gender, body mass index (BMI), family history, duration of diabetes, duration of neuropathy symptoms, smoking & alcohol drinking.

**Table 1 .Demographic characteristics of patients with diabetic neuropathy.**

Demographic characters		Group 1		Group 2		P-value <sup>©</sup>
		N	(%)	N	(%)	
Age (years)	$\leq$ 60	7	(14)	8	16()	0.942 <sup>NS</sup>
	$>$ 60	9	(18)	9	(18)	
Gender	Male	8	(16)	5	(10)	0.426 <sup>NS</sup>
	Female	8	(16)	12	(24)	
BMI (kg/m <sup>2</sup> )	$<$ 18.5	0	(0)	0	(0)	0.087 <sup>NS</sup>
	17.5-25	4	(8)	0	(0)	
	$>$ 25	12	(24)	17	(34)	
Family History	Yes	14	(28)	11	(22)	0.246 <sup>NS</sup>
Duration of neuropathy symptoms	$<$ 1 year	3	(6)	1	(2)	0.679 <sup>NS</sup>
	1-5 years	9	(18)	12	(24)	
	$>$ 5 years	4	(8)	4	(8)	
Duration of Diabetes	$<$ 10 years	1	(2)	3	(6)	0.390 <sup>NS</sup>
	$\geq$ 10 years	15	(30)	14	(28)	
Smoking	Yes	3	(6)	7	(14)	0.802 <sup>NS</sup>
Alcohol	Yes	0	(0)	0	(0)	1.000 <sup>NS</sup>

The data is shown as (N): Number of patients, and (%): Percentage.

<sup>©</sup>Chi square test ( $\chi^2$ ) test for goodness of fit used to test counts between groups,

NS: P value  $>$  0.05 is considered no significant differences.

As can be seen in Table (2) and Figure (1) the results demonstrated a significant difference (P $<$ 0.05) in Michigan Neuropathy Screening Instrument (MNSI) score between the two groups at

the completion of the study. However, there was a highly significant improvement (P $<$ 0.01) within each study group after 3 months of treatment.

**Table 2. Effect of treatment on MNSI in patients with diabetic neuropathy.**

		Group 1	Group 2	P-Value <sup>a</sup>
MNSI score	Pre	11.25 $\pm$ 1.29	11.24 $\pm$ 1.09	0.972 <sup>NS</sup>
	Post	8.81 $\pm$ 1.17	9.53 $\pm$ 0.72	0.045 <sup>*</sup>
P-Value <sup>b</sup>		0.001 <sup>**</sup>	0.001 <sup>**</sup>	

Data is presented in the form of mean  $\pm$  SD, <sup>a</sup> Independent t test used to test statistical differences between groups (Horizontally), <sup>b</sup> paired t-test used to compare between pre and post within each group. NS: No significant differences (p $\geq$ 0.05), (<sup>\*</sup>) significant differences (p $<$ 0.05), (<sup>\*\*</sup>) highly significant differences (p $<$ 0.01).

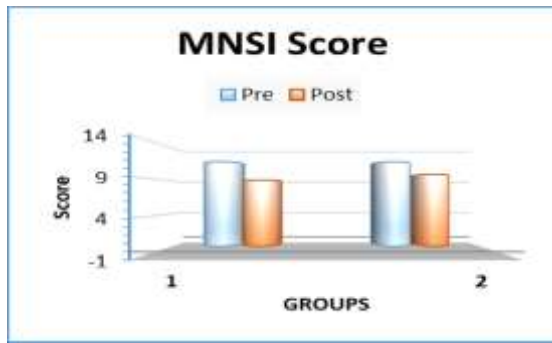


Figure 1. Effect of treatment on MNSI in Patients with diabetic neuropathy.

At the end of the trial, there were no significant variations in FBG and HbA<sub>1c</sub> levels between the two groups ( $P \geq 0.05$ ). However, patients received coenzyme Q10 in addition to gabapentin group (2) demonstrated a significant and highly significant decrease in the FBG & HbA<sub>1c</sub> levels, respectively. While no significant reductions were reported in group 1 for both FBG & HbA<sub>1c</sub> levels at the finish of the study.

Table 3. Effect of treatment on FBG & HbA<sub>1c</sub> levels in patients with diabetic neuropathy.

Study Groups		Group 1		Group 2		P-Value <sup>a</sup>
FBG	Pre	225.94 ±	90.98	203.59 ±	64.87	0.426 <sup>NS</sup>
	Post	188.69 ±	94.69	162.59 ±	53.79	0.344 <sup>NS</sup>
P-Value <sup>b</sup>		0.08 <sup>NS</sup>		0.013*		
HbA1	Pre	9.09 ±	1.36	9.51 ±	1.17	0.360 <sup>NS</sup>
	Post	8.73 ±	1.14	8.22 ±	0.79	0.129 <sup>NS</sup>
P-Value <sup>b</sup>		0.41 <sup>NS</sup>		0.001**		

Data presented as mean ± SD, <sup>a</sup> Independent t test used to test statistical differences between groups (Horizontally), <sup>b</sup> paired t-test used to compare between pre and post within each group. NS: No significant differences ( $p \geq 0.05$ ), (\*) significant differences ( $p < 0.05$ ), \*\* highly significant differences ( $p < 0.01$ ).

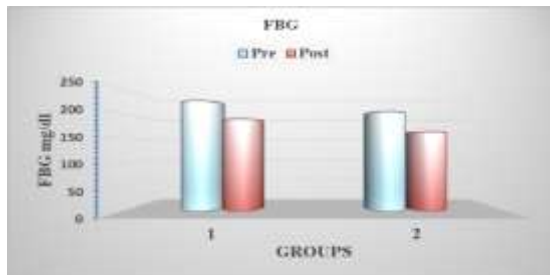


Figure 2. Effect of treatment on FBG level in patients with diabetic neuropathy.

considerable variances ( $P < 0.05$ ) in TNF- $\alpha$ , IL-6 & SOD levels at the end of the study between both groups. Meanwhile, highly significant reductions were noticed in the levels of these three parameters after completing the study in respect to pretreatment levels, which are clearly shown in Table (4) and Figure (4, 5, & 6).

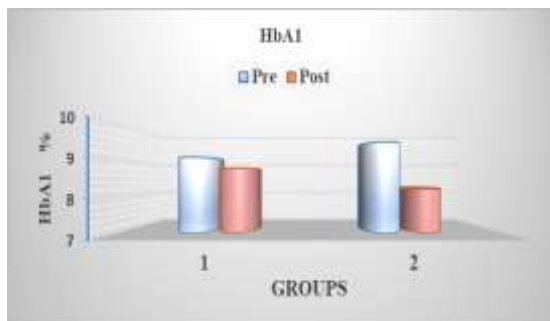


Figure 3. Effect of treatment on HbA<sub>1c</sub> level in patients with diabetic neuropathy.

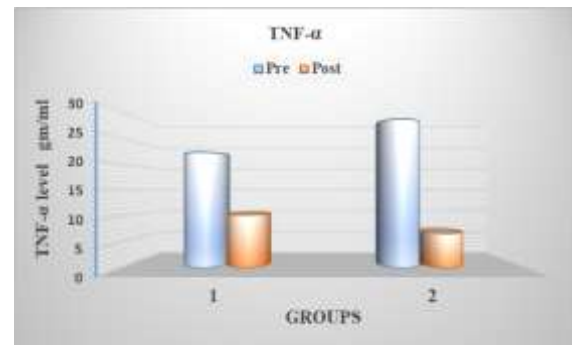


Figure 4. Effect of treatment on TNF- $\alpha$  levels in patients with diabetic neuropathy.

Regarding to the anti-inflammatory and antioxidant effect of adding coenzyme Q10 to gabapentin treatment of diabetic neuropathy, TNF- $\alpha$ , IL-6 and SOD levels were measured. The findings of this research revealed that there are

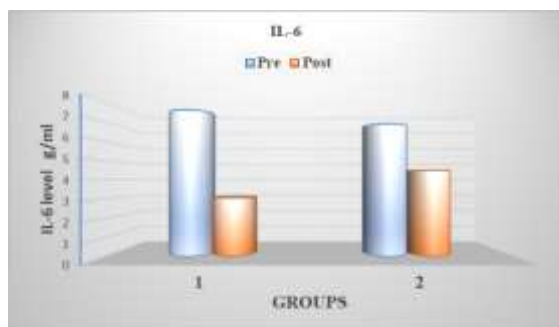


Figure 5. Effect of treatment on IL-6 levels in patients with diabetic neuropathy.

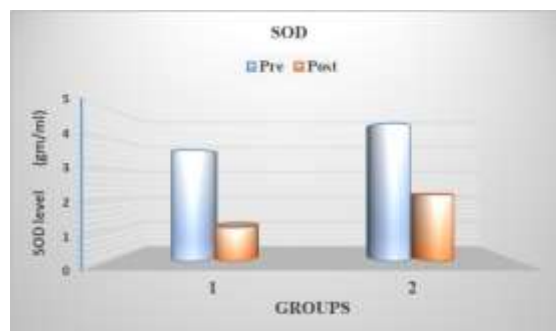


Figure 6. Effect of treatment on SOD levels in patients with diabetic neuropathy.

Table 4. Effect of treatment on TNF- $\alpha$ , IL-6 & SOD in patients with diabetic neuropathy.

Study Groups		Group 1			Group 2			P-Value <sup>a</sup>
TNF- $\alpha$	Pre	22.26	±	10.7	28.65	±	10.4	0.092 <sup>NS</sup>
	Post	10.20	±	4.65	6.63	±	2.42	0.012 <sup>*</sup>
P-Value <sup>b</sup>		0.001 <sup>**</sup>			*,*,*,\ **			
IL-6	Pre	7.65	±	5.04	6.93	±	1.75	0.594 <sup>NS</sup>
	Post	3.05	±	1.39	4.50	±	1.37	0.002 <sup>*</sup>
P-Value <sup>b</sup>		0.004 <sup>**</sup>			*,*,*,\ **			
SOD	Pre	3.62	±	1.79	4.49	±	2.83	0.295 <sup>NS</sup>
	Post	1.10	±	0.641	2.17	±	1.63	0.020 <sup>*</sup>
P-Value <sup>b</sup>		0.001 <sup>**</sup>			0.001 <sup>**</sup>			

Data presented as mean  $\pm$  SD, <sup>a</sup> Independent t test used to test statistical differences between groups (Horizontally), <sup>b</sup> paired t-test used to compare between pre and post within each group. NS: No significant differences ( $p \geq 0.05$ ), (\*) significant differences ( $p < 0.05$ ), \*\* highly significant differences ( $p < 0.01$ ).

## Discussion

Considering demographic and disease characteristic of the studied patients, the average age of the study's participants was 60.26 years. Even though deals with a small sample of population, the mean of age is similar to that reported in other studies<sup>(15, 16)</sup>. This is attributed to the fact that incidence of neuropathy increased with advanced age<sup>(17)</sup>. The duration of time a person had diabetes was  $(10.43 \pm 3.42)$  years old; Long-term diabetics are predisposed to develop neuropathy due to prolonged exposure of peripheral nerves to hyperglycemia. The current evidence supports the involvement of glycemic management in the development and progression of DN.<sup>(18)</sup> Within the present study significant ( $p < 0.05$ ) difference in MNSI score was noticed after 90 days of treatment between the groups. In this study, CoQ10 therapy provided early onset of clinically relevant pain reduction with only minimal and probably avoidable side effects. Gabapentin mono therapy is a viable treatment option for people with neuropathic pain who have limited treatment options. It has advantages over currently available medications as a first-line treatment<sup>(19)</sup>. These improvements could

be due to gabapentin's one-of-a-kind action on calcium channels and consequently neurotransmitter release. Gabapentin may be due to its anticonvulsants effects, acts predominantly on calcium channels & regulates the release of numerous neurotransmitters in the CNS, which may result in gabapentin having a better influence<sup>(20)</sup>. In a recent study, a clear link was shown between improved glycemic control and diabetes patients<sup>(21)</sup>. Many studies have revealed that CoQ10 has beneficial impacts on glucose homeostasis measures. Schroeder *et al.*, for example, demonstrated that CoQ10 as an antioxidant therapy may reduce glucose levels by protecting  $\beta$  cells from ROS and glucose toxicity, as well as increasing insulin production<sup>(22)</sup>. Furthermore, CoQ10 reduces insulin resistance via modulating insulin as well as adiponectin receptors, along with glucose transporters, tyrosine kinase (TK), and phosphatidylinositol kinase (PI3 K), and also the redox system, soluble receptor of advanced glycosylated end products (sRAGE), as well as adipocytokines<sup>(23)</sup>.

The current investigation found that the levels of IL-6, TNF- $\alpha$ , and SOD were significantly lowered

compared to baseline. These effects of CoQ10 on cytokines are due to its anti-inflammatory properties. The exact mechanisms are unknown. However, CoQ10 has the ability to block the activation of the NF-KB signaling pathway as well as neutralize free radicals. <sup>(24)</sup>. In addition, CoQ10 has been shown to have anti-inflammatory properties through decrease the release of pro-inflammatory cytokines and COX-2 expression during inflammatory injury <sup>(25, 26)</sup>

In the present study showed, elevation in SOD enzyme activity at baseline, This suggested that diabetes individuals' superoxide radical generation may be increased as a result of oxidative stress caused by high glucose levels <sup>(27)</sup>. Oral CoQ10 supplement did not result in an increased SOD level, in fact it was decreased in both group rather than increased.

This finding may be due to a number of reasons, the slightest variation in lipid peroxidation and antioxidant enzyme activity could be influenced by glucose management <sup>(27)</sup> & CoQ10, as an antioxidant and free-radical scavenger, may help to reduce oxidative stress in the central and peripheral neurological systems <sup>(28)</sup>.

Tsai *et al.* found that supplementing with CoQ10 increased SOD activity <sup>(29)</sup> and Chio *et al* <sup>(30)</sup>.

## Conclusion

Addition of CoQ10 to gabapentin in diabetic neuropathy patients resulted in improving pain, physical activity and the glycemic control of patients, it is probably helpful in reducing severity and progression of neuropathy by reducing the impact of inflammation and oxidative stress.

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