

# Potential Impact of Quercetin as Adjuvant Therapy to Gabapentin on Norfolk Quality of Life for Diabetic Neuropathy Patients

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## Abstract

Metabolic imbalances that are activated in the diabetic environment of hyperglycemia, dyslipidemia and impaired of the insulin signaling are considered the key players in the development of diabetic neuropathy (DN). Animal studies have shown that, quercetin (QUR) could significantly improve both of hyperglycemia and insulin resistance. Therefore, QUR could effectively improve hyperglycemia, and anti-oxidation status in type 2 diabetes mellitus (T2DM). A sample consist of 40 participants enrolled randomly into two groups; group A, 20 patients treated with gabapentin capsules 300 mg once daily at night for 3 consecutive months, and group B, 20 patients treated with gabapentin capsules 300 mg once daily at night plus quercetin 500 mg twice daily for 3 consecutive months. Adding quercetin is slightly better than dispensing gabapentin alone in relating to total Norfolk quality of life for diabetic neuropathy (Norfolk QOL-DN). Adding quercetin is very slightly better than dispensing gabapentin alone in relating to both of physical functioning/large fibers neuropathy domain and small fibers neuropathy domain. Some superiority of adding quercetin despite the insignificant p-value among the two groups in relating to both of activities of daily living domain and symptoms domain. Adding quercetin is slightly better than gabapentin alone in relating to autonomic neuropathy domain. Quercetin is better in increasing insulin secretion due to the highest C-peptide level beside a small degree in improving insulin sensitivity, as evidenced by failed to decrease fasting serum glucose, decreased HbA1c despite insignificant p-value, increased insulin level insignificantly, and increased C-peptide level significantly. The conclusion of this study is adding quercetin to patients with diabetic neuropathy has a slightly improving effect on Norfolk QOL-DN and has significant improving effect on increasing insulin secretion.

**Keywords:** diabetic neuropathy, Norfolk quality of life for diabetic neuropathy, and quercetin.

## 1. Introduction

Type 2 diabetes is a group of metabolic syndromes that is characterized by absolute or relative insulin secretion insufficiency and decreased sensitivity of the target organs to insulin, followed by fat, protein, electrolytes, water and other metabolic disorders (1). Diabetes impacts public healthcare expenditures worldwide with an estimated cost of more than \$827 billion (2). Type 2 diabetes mellitus (T2DM) is associated with decrease in quality of life (3). Diabetic neuropathy can be classified as autonomic and somatic (diabetic peripheral neuropathy) (4,5). The pathogenesis of diabetic neuropathy (DN) is multifactorial. Metabolic imbalances in the peripheral nervous system (PNS) that are activated in the diabetic environment of hyperglycemia, dyslipidemia and impaired of the insulin signaling are considered the key players in the development of DN (6). In the acute metabolic state, any excess in the intracellular glucose is metabolized by one of the

following three pathways: glycolysis, the polyol pathway, or the hexosamine pathway. Activation of these pathways can lead to initiation of inflammatory cascades and formation of reactive oxygen species (ROS), which can induce oxidative stress (OS) and disrupt nerve energy supply (7). Activation of these metabolic pathways eventually result in oxidative stress and inflammatory stress in neurons and the adjacent microvascular system (6).

Gabapentin (brand-name Neurontin®; Pfizer) is approved by FDA for treatment of epilepsy and post-herpetic neuralgia, and—in its prodrug version—for restless legs syndrome (8-10). Gabapentin is effective for the treatment of painful diabetic neuropathy (11). Quercetin (QUR) is the most studied bioactive flavonoids, shown significantly beneficial effects on different diseases (12,13). Animal studies have shown that, quercetin could significantly improve both of hyperglycemia and insulin resistance. The underlying mechanism is associated with a reduction in oxidative stress, pancreatic endoplasmic reticulum (ER) stress, and  $\beta$ -cell death.

Therefore, QUR could effectively improve hyperglycemia, and anti-oxidation status in T2DM (14-18).

This study designed to evaluate the effects of quercetin as adjuvant therapy to gabapentin in patients with diabetic neuropathy on the followings; Norfolk quality of life for diabetic neuropathy (Norfolk QOL-DN), glycemic control, and finding the regression correlations among Norfolk QOL-DN, glycemic control parameters, and some of both demographic data and disease characteristics.

## 2. Patients and Methods

A randomized single-blind clinical trial was performed at the Specialized Center for Endocrine Diseases and Diabetes Baghdad/Al-Russafa in Baghdad, Iraq. Diabetic patients who were visited the center were approached and the selection of patients based on the presence of mild to moderate diabetic neuropathy. Patients were fully informed of the clinical trial protocol and a written consent was obtained from the patients before starting the clinical trial. Ethical and scientific committee in Baghdad Al-Russafa Health Directorate approved the clinical trial. The sample consist of forty participants enrolled randomly and subdivided into two groups. The inclusion criteria of this clinical trial are the following: (1) patients with type 2 diabetes mellitus aged 30-65 years old, (2) mild to moderate diabetic neuropathy. The exclusion criteria of this clinical trial are the following: (1) type 1 diabetic patients, (2) severe diabetic neuropathy, (3) presence of endocrine or gynecological diseases, (4) hypersensitivity to any drug or supplement that used in this clinical trial, (5) pregnancy and breastfeeding. Patients were categorized randomly into 2 groups; group A, twenty patients treated with gabapentin cap. 300 mg once daily at night for three consecutive months, and group B, twenty patients treated with gabapentin caps. 300 mg once daily at night + quercetin 500 g twice daily for three consecutive months.

Quality of life (QOL) was measured by using the 35-item Norfolk Quality of Life for Diabetic Neuropathy (Norfolk QOL-DN) questionnaire. The questionnaire was interpreted into Arabic when interviewed the patients.

Norfolk QOL-DN is designed to capture and quantify the impact of diabetic neuropathy on the quality of life of individual patients with diabetic neuropathy. Fourteen of the items are of a health-related, biographical nature and are not scored. These are on the front page, and they are not numbered nor scored. The Norfolk QOL-DN instrument in this study was composed of 35 items. Items 1–7 (Part I) are nerve fiber-related symptoms (numbness, tingling/pins and needles, electric shocks, other unusual sensations, superficial peripheral pain, deep pain, and weakness). With items 8–35 (Part II), subjects respond to questions about the degree of physical problems that interfere with their activities of daily living (ADLs). These items are scored on a

five-point Likert scale (0, "No Problem"; to 4, "Severe Problem"), while Questions 31 and 32 are scored in a different way (19).

The patient answered the questionnaire in a quiet lone area in the room of post-graduates in the specialized center, and were free of distractions, and encouraged to answer the questions precisely by giving them an enough time. All questions were answered with no missing data.

The scales were determined based on an exploratory factor analysis, so the questions have loaded into their respective domains. All symptoms (1-7) (Part I) are scored as either a 1 or a 0, indicating that a presence or absence of a symptom. Except for Questions 31, and 32, the other items 8–35 (Part II) are scored according to the five-point Likert Scale (0, "No Problem"; to 4, "Severe Problem"). In Question 31, the middle item, "Good", is scored as 0, "Very Good" is scored as –1, "Excellent" is scored as –2, "Fair" is scored as 1, and "Poor" is scored as 2. In Question 32, the middle item, "About the Same", is scored as 0, "Somewhat better" is scored as –1, "Much better" is scored as –2, "Somewhat worse" is scored as 1, and "Much worse" is scored as 2.

The total quality of life (QOL) and five domains should be summed as follows:

Total quality of life (QOL)  $\sum$  (1-7, 8-35)

Physical functioning/Large fiber neuropathy  $\sum$  (8, 11, 13-15, 24, 27-35)

Activities of daily living (ADLs)  $\sum$  (12, 22-23, 25-26)

Symptoms  $\sum$  (1-7, 9)

Small fiber neuropathy  $\sum$  (10, 16-18)

Autonomic neuropathy  $\sum$  (19-21)

After 8 hours fasting, 10 ml of venous blood were withdrawn from each patient at baseline pre-treatment and after 90 days' post-treatment by using 10 ml syringe. In a tube containing ethylenediaminetetracetic acid (EDTA) (1.5 mg/ml), 3 ml of the withdrawn blood was putted in it and stored in a refrigerator at a degree from +2°C to +8°C for analysis of glycated hemoglobin (HbA1c) within 1 week. In a gel tube, 7 ml of the withdrawn blood was putted in it and leaved a while for clotting and then centrifuged for 15 minutes at speed of 3000 rpm to separate serum. In an Eppendorf tube, serum samples were divided by micropipette and kept frozen at a degree –20°C until the end of the clinical trial to measure the required parameters.

The analysis of the data done by using the Statistical Package for the Social Sciences (SPSS) software, version 28.0. As well as data were subjected to Shairo test for checking its normal distribution.

## 3. Results

In table (1), demographic characteristics and socioeconomic status were presented. No statistically significant differences were found between the values of the study groups in relating to age (in years), gender, body mass index (kg/m<sup>2</sup>), waist circumference (in cm), blood groups, level of education, monthly income (in dollars), smoking habits, and alcohol drinking.

**Table (1): Demographic characteristics and socioeconomic status.**

Demographic character or socioeconomic status		Group A	Group B	P-value
		N (%)	N (%)	
Age (years)	≤ 50	8 (20.0)	6 (15.0)	0.507 NS b
	> 50	12 (30.0)	14 (35.0)	
Gender	Male	10 (25.0)	6 (15.0)	0.197 NS b
	Female	10 (25.0)	14 (35.0)	
BMI (kg/m <sup>2</sup> )	≤ 18.4	1 (2.5)	0 (0.0)	0.328 NS <sup>a</sup>
	18.5 – 24.9	10 (25.0)	6 (15.0)	
	25 – 29.9	4 (10.0)	5 (12.5)	
	≥ 30	5 (12.5)	9 (22.5)	
Waist circumference (cm)	Male	< 102	9 (22.5)	0.247 NS <sup>a</sup>
		≥ 102	1 (2.5)	
	Female	< 88	1 (2.5)	
		≥ 88	9 (22.5)	
Blood group	Rh+	A	2 (5.0)	0.421 NS <sup>a</sup>
		B	5 (8.5)	
		AB	2 (5.0)	
		O	10 (25.0)	
	Rh-	A	1 (2.5)	
Educational level	Illiterate	4 (10.0)	2 (5.0)	0.446 NS <sup>a</sup>
	Primary	8 (20.0)	12 (30.0)	
	Secondary	6 (15.0)	3 (7.5)	
	College	2 (5.0)	3 (7.5)	
Monthly income (dollars)	< \$500	11 (27.5)	12 (30.0)	0.466 NS <sup>a</sup>
	\$500-1000	7 (17.5)	4 (10.0)	
	> \$1000	2 (5.0)	4 (10.0)	
Smoking	Yes	4 (10.0)	1 (2.5)	0.151 NS <sup>a</sup>
Alcohol drinking	Yes	1 (100)	0 (0)	1.000 NS <sup>a</sup>

Data presented as (N): Number of patients, (%) Percentage. <sup>a</sup> Fisher's Exact test used to assess differences of parameters between groups, b Chi square test to assess differences in categorical variables. NS: No significant changes (p≥0.05). BMI: body mass index, kg/m<sup>2</sup>: kilogram per square meter, cm: centimeter, Rh: Rhesus factor.

In table (2), disease characteristics were presented. No statistically significant differences were found between the values of the study groups in relating to duration of diabetes mellitus (years), duration of

diabetic neuropathy (years), family history of diabetes mellitus, family history of diabetic neuropathy, medications used, presence or absence of comorbidity(s), and number of that comorbidities.

**Table (2): Disease characteristics.**

Disease character		Group A	Group B	P-value
		N (%)	N (%)	
Duration of DM (years)	< 1	0 (0.0)	0 (0.0)	0.362 NS <sup>a</sup>
	1 – ≤ 5	5 (12.5)	3 (7.5)	
	> 5 – 10	4 (10.0)	8 (20.0)	
	> 10	11 (27.5)	9 (22.5)	
Duration of DN (years)	< 1	3 (7.5)	3 (7.5)	0.889 NS <sup>a</sup>
	1 – ≤ 5	14 (35.0)	15 (37.5)	
	> 5 – 10	3 (7.5)	2 (5.0)	
	> 10	0 (0.0)	0 (0.0)	
Family history of DM	Yes	17 (42.5)	14 (35.0)	0.451 NS <sup>a</sup>
	No	3 (7.5)	6 (15.0)	
Family history of DN	Yes	10 (25.0)	9 (22.5)	0.751 NS b
	No	10 (25.0)	11 (27.5)	
Medications used	OHA	3 (7.5)	6 (15.0)	0.451 NS <sup>a</sup>
	OHA + insulin	17 (42.5)	14 (35.0)	
Presence of comorbidity(s)	Yes	13 (32.5)	11 (27.5)	0.518 NS b
	No	7 (17.5)	9 (22.5)	
Number of comorbidities (Mean ± SD)		1.5 ± 0.7	1.9 ± 1.0	0.174 NS c

Data presented as (N): Number of patients, (%) Percentage. <sup>a</sup> Fisher's Exact test used to assess differences of parameters between groups, b Chi square test to assess differences in categorical variables c T-test used to assess number of comorbidities between groups. NS: No significant changes (p≥0.05), SD: standard deviation. DM: diabetes mellitus, DN: diabetic neuropathy, OHA: oral hypoglycemic agents.

The effect of treatment on Norfolk quality of life for

diabetic neuropathy (Norfolk QOL-DN) were demonstrated in table (3), there is a highly significant

reduction ( $p < 0.01$ ) in the two groups in relating to physical functioning / large fibers neuropathy domain after finishing the treatment courses. Moreover, there was a highly significant reduction ( $p < 0.01$ ) in group B and a significant reduction ( $p < 0.05$ ) in group A in relating to activities of daily living (ADLs) domain after finishing the treatment courses. As well as there was a highly significant reduction ( $p < 0.01$ ) in the two groups in relating to symptoms domain after finishing the treatment courses. Moreover, there was a highly

significant reduction ( $p < 0.01$ ) in the two groups in relating to small fibers neuropathy domain after finishing the treatment courses. As well as there was a significant reduction ( $p < 0.05$ ) in the two groups in relating to autonomic neuropathy domain after finishing the treatment courses. Furthermore, there was a highly significant reduction ( $p < 0.01$ ) in the two groups in relating to QOL as a total of five domains involving of 35 questions.

**Table (3): Effect of treatment on Norfolk quality of life for diabetic neuropathy.**

Domain	Patient Groups			P-Value a
		Group A	Group B	
		M (±SD)	M (±SD)	
Physical functioning / Large fibers neuropathy	Pre	31.4 (±14.2)	24.9 (±14.2)	0.078 NS
	Post	23.3 (±16)	16.1 (±11.6)	0.055 NS
P-Value b		< 0.001**	< 0.001**	
Activities of daily living (ADLs)	pre	7.1 (±6.9)	6.5 (±6.1)	0.377 NS
	Post	5.4 (±6.2)	4.6 (±4.6)	0.323 NS
P-Value b		0.010*	0.001**	
Symptoms	Pre	6.4 (±1.6)	6.5 (±1.8)	0.390 NS
	Post	5.1 (±1.4)	4.7 (±1.7)	0.209 NS
P-Value b		< 0.001**	< 0.001**	
Small fibers neuropathy	Pre	5 (±3.3)	4.4 (±3.5)	0.290NS
	Post	3.5 (±3.4)	2.9 (±2.7)	0.253 NS
P-Value b		< 0.001**	< 0.001**	
Autonomic neuropathy	Pre	3.3 (±2.3)	2.7 (±2.5)	0.239 NS
	Post	2.4 (±1.7)	1.9 (±1.9)	0.192NS
P-Value b		0.003*	0.004*	
Total quality of life (QOL)	Pre	53.1 (±24.2)	44.9 (±24.1)	0.146 NS
	Post	39.7 (±25.9)	30.2 (±19.7)	0.097 NS
P-Value b		< 0.001**	< 0.001**	

Data presented as mean ± SD, a T-test used to assess differences between groups (horizontally), b Paired T-test for comparison between Pre and Post within each group. NS: No significant changes ( $p \geq 0.05$ ), (\*) significant changes ( $p < 0.05$ ), \*\* highly significant changes ( $p < 0.01$ ).

The effect of treatment on glycemic control showed in table (4). A significant difference ( $p < 0.05$ ) was found between the study groups in in relating to values of baseline fasting serum glucose (FSG) and a highly significant difference ( $p < 0.01$ ) was found in relating to values of post-treatment FSG. In addition, in both of group A and group B, a significant increase ( $p < 0.05$ ) was found in FSG values after three months of treatment. Moreover, there was an insignificant

decrease in relating to values of glycated hemoglobin in the two groups. As well as a significant difference ( $p < 0.05$ ) between the study groups in values of insulin was found only after finishing the treatment courses. Also, a significant difference ( $p < 0.05$ ) between the study groups in values of C-peptide was found only at the end of treatment courses. Moreover, a highly significant increase ( $p < 0.01$ ) in C-peptide values in group B after 3 months of treatment was found.

**Table (4): Effect of treatment on glycemic control.**

Parameter		Group A	Group B	P-value a
		M (±SD)	M (±SD)	
FBG (mmol/L)	Pre	12.32 (± 5.03)	9.26 (± 3.39)	0.015*
	Post	16.03 (± 5.52)	10.78 (± 3.18)	< 0.001**
P-value b		0.024*	0.025*	
HbA1c (%)	Pre	9.74 (± 2.12)	9.04 (± 1.92)	0.139 NS
	Post	9.39 (± 2.1)	8.42 (± 1.76)	0.060NS
P-value b		0.497 NS	0.109 NS	
Insulin (µIU/L)	Pre	13.2 (± 5.22)	14.61 (± 7.2)	0.274 NS
	Post	12.48 (± 4.86)	15.9 (± 6.26)	0.042*
P-value b		0.637 NS	0.284 NS	
C-peptide (ng/mL)	Pre	2.86 (± 1.04)	3.08 (± 1)	0.316 NS
	Post	3.44 (± 1.57)	4.73 (± 1.52)	0.005*
P-value b		0.130 NS	< 0.001**	

Data presented as mean ± SD, a T-test used to assess differences between groups (horizontally), b Paired T-test for comparison between Pre and Post within each group. NS: No significant changes ( $p \geq 0.05$ ), \* significant changes ( $p < 0.05$ ), \*\* highly significant changes ( $p < 0.01$ ). FSG: fasting serum glucose, HbA1c: glycated hemoglobin.

There were no significant correlations among Norfolk quality of life for diabetic neuropathy vs. glycemic control parameters (FSG, HbA1c, insulin and C-peptide) for group A, as presented in table (5A). There was a strong positive relationship between Norfolk QOL-DN and body mass index for group A, where the correlation is significant at the 0.05 level (2-tailed). In addition, there was a medium

association between Norfolk QOL-DN and gender, where the correlation is significant at the 0.05 level (2-tailed), as presented in table (5B). There were insignificant correlations among Norfolk QOL-DN vs. some disease characteristics (duration of DM, duration of DN, family history of DM, family history of DN, and number of comorbidities) for group A, as presented in table (5C).

**Table (5A): Correlations among Norfolk quality of life for diabetic neuropathy vs. glycemic control parameters for group A.**

P-value & R a		FBG	HbA1c	Insulin	C-peptide
Norfolk QOL-DN	Correlation Coefficient (R)	-0.175	0.203	-0.257	-0.287
	P-value	0.230	0.195	0.137	0.110

a Pearson's r correlation & simple linear regression used for the grouped data to find Correlation Coefficient (R) and P-value (linear relationship). FBG: fasting blood glucose, HbA1c: glycated hemoglobin, Norfolk QOL-DN: Norfolk quality of life for diabetic neuropathy.

**Table (5B): Correlations among Norfolk quality of life for diabetic neuropathy vs. some demographic data for group A.**

		Age a	BMI a	WCF a	Gender b	Educational level b	Income b
Norfolk QOL-DN	Correlation Coefficient (R)	-0.015	0.517*	0.356	0.430*	0.250	0.075
	P-value	0.475	0.010	0.062	0.029	0.144	0.377

a Pearson's r correlation & simple linear regression used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association for linear relationship). b Eta Coefficient test r correlation, & T.test used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association between a categorical variable and a scale- or interval-level variable). \* Correlation is significant at the 0.05 level (2-tailed). BMI: body mass index, Norfolk QOL-DN: Norfolk quality of life for diabetic neuropathy, WCF: waist circumference.

**Table (5C): Correlations among Norfolk quality of life for diabetic neuropathy vs. some disease characteristics for group A.**

		Duration of DM a	Duration of DN a	Family history of DM b	Family history of DN b	Number of comorbidities a
Norfolk QOL-DN	Correlation Coefficient (R)	-0.040	0.420	0.275	0.259	0.032
	P-value	0.434	0.032	0.121	0.135	0.447

a Pearson's r correlation & simple linear regression used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association for linear relationship). b Eta Coefficient test r correlation & T-test used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association between a categorical variable and a scale- or interval-level variable). DM: diabetes mellitus, DN: diabetic neuropathy, Norfolk QOL-DN: Norfolk quality of life for diabetic neuropathy.

Furthermore, a strong positive relationship between C-peptide and Norfolk QOL-DN was found for group B, where its correlation is significant at the 0.05 level (2-tailed), as showed in table (6A). A very strong negative relationship between age and Norfolk QOL-DN was found for group B, where its correlation is significant at the 0.01 level (2-tailed). However, there were strong association among

Norfolk QOL-DN with all of gender, educational level and income, where the correlation is significant at the 0.01 level (2-tailed), as presented in table (6B). There were insignificant correlations among Norfolk QOL-DN vs. some disease characteristics (duration of DM, duration of DN, family history of DM, family history of DN, and number of comorbidities) for group B, as presented in table (6C).

**Table (6A): Correlations among Norfolk quality of life for diabetic neuropathy vs. glycemic control parameters for group B.**

P-value & R a		FBG	HbA1c	Insulin	C-peptide
Norfolk QOL-DN	Correlation Coefficient (R)	0.375	0.191	-0.227	0.418*
	P-value	0.051	0.209	0.168	0.033

a Pearson's r correlation & simple linear regression used for the grouped data to find Correlation Coefficient (R) and P-value (linear relationship). \* Correlation is significant at the 0.05 level (2-tailed). FBG: fasting blood glucose, HbA1c: glycated hemoglobin, Norfolk QOL-DN: Norfolk quality of life for diabetic neuropathy.

**Table (6B): Correlations among Norfolk quality of life for diabetic neuropathy vs. some demographic data for group B.**

		Age a	BMI a	WCF a	Gender b	Educational level b	Income b
Norfolk QOL-DN	Correlation Coefficient (R)	-0.593**	0.072	0.068	0.629**	0.582**	0.620**
	P-value	0.003	0.381	0.389	0.001	0.004	0.002

a Pearson's r correlation & simple linear regression used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association for linear relationship). b Eta Coefficient test r correlation, & T-test used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association between a categorical variable and a scale- or interval-level variable). \*\* Correlation is significant at the 0.01 level (2-tailed). BMI: body mass index, Norfolk QOL-DN: Norfolk quality of life for diabetic neuropathy, WCF: waist circumference.

**Table (6C): Correlations among Norfolk quality of life for diabetic neuropathy vs. some disease characteristics for group B.**

		Duration of DM a		Duration of DN a	Family history of DM b	Family history of DN b	Number of comorbidities a
Norfolk QOL-DN	Correlation Coefficient (R)	-0.342		0.245	0.307	0.123	0.312
	P-value	0.070		0.148	0.094	0.302	0.090

a Pearson's r correlation & simple linear regression used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association for linear relationship). b Eta Coefficient test r correlation & T-test used for the grouped data to find Correlation Coefficient (R) and P-value (strength of association between a categorical variable and a scale- or interval-level variable). DM: diabetes mellitus, DN: diabetic neuropathy, Norfolk QOL-DN: Norfolk quality of life for diabetic neuropathy.

#### 4. Discussion

Generic instruments such as the short forms (SF-36 and SF-12) and EuroQol- 5 Dimension (EQ-5D) are nonspecific and known to lack sensitivity and specificity to disease-specific aspects of health-related quality of life (HRQL) (20,21). Therefore, a disease-specific measure is needed to evaluate HRQL. Norfolk QoL-DN has been documented to have good sensitivity and specificity, as well as have good positive and negative predictive values, strongly suggesting its use for diabetic neuropathy (22). The Norfolk QOL-DN is a comprehensive nerve fiber-specific questionnaire and validated assessment tool, specific to peripheral diabetic neuropathy, captures the whole spectrum of PDN, comprising of five domains representing separated neuropathic disabilities which are referred to different nerve fibers (21,23-28). The total Norfolk QOL-DN score has been shown to correlate generally with the total neuropathy score (TNS) (22,23). There is no study investigate the effect of quercetin on Norfolk QOL-DN based on searching on PubMed, The Cochrane Library, and MEDLINE websites. The current novel study is the first study that investigate these effects.

In the present study, post-treatment total Norfolk QOL-DN is 39.7 (±25.9), and 30.2 (±19.7) for group A and B respectively; where the range of possible score for total Norfolk QOL-DN is (-4) – 115 (the negative value arises from the questions 31 and 32); indicating that, adding quercetin is slightly better than dispensing gabapentin alone. Post-treatment physical functioning/large fibers neuropathy domain is 23.3 (±16), and 16.1 (±11.6) for group A and B respectively; where the range of possible score is (-4) – 56; indicating that, adding quercetin is very

slightly better than dispensing gabapentin alone. Post-treatment activities of daily living (ADLs) domain are 5.4 (±6.2), and 4.6 (±4.6) for group A and B respectively; where the range of possible score is 0 – 20; indicating some superiority of adding quercetin despite the insignificant p-value among the two groups. Post-treatment symptoms domain is 5.1 (±1.4), and 4.7 (±1.7) for group A and B respectively; where the range of possible score is 0 – 11; indicating some superiority of adding quercetin despite the insignificant p-value among the two groups. Post-treatment small fibers neuropathy domain is 3.5 (±3.4), and 2.9 (±2.7) for group A and B respectively; where the range of possible score is 0 – 16; indicating that, adding quercetin has very slightly additional effect than gabapentin alone. Post-treatment autonomic neuropathy domain is 2.4 (±1.7), and 1.9 (±1.9) for group A and B respectively; where the range of possible score is 0 – 12; indicating that, adding quercetin is slightly better than dispensing gabapentin alone.

Several studies have reported that quercetin has antidiabetic effect by upregulates insulin secretion and C-peptide, decreases FBG and improves hyperglycemia, attenuates insulin resistance, and decreases HbA1c (29-33). A study has investigated the hypoglycemic effect of quercetin on human and found that quercetin improved the amount of insulin and blood glucose (34).

Quercetin exerts antidiabetic activity via the following mechanisms; inhibits nuclear factor kappa B (NF-κB) activity in pancreatic β-cells and thereby inhibit the generation of inflammatory cytokines (35,36); activates sirtuin 1 (SIRT1) via improving the NAD+ level; attenuates blood glucose level via increasing phosphorylation of Akt (regulated by SIRT1) and glycogen synthase kinase 3 (GSK-3)

(34,36,37); and increases glucose uptake via enhancement of AMP-activated protein kinase (AMPK) activation and upregulation of glucose transporter type 4 (GLUT4); AMPK decreases the expression of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxylase (PEPCK) resulting in attenuation of glucose outcome (35,38,39).

Other proposed mechanisms of quercetin are involving, decreasing of glucose absorption in the small intestine by decreasing effects of maltase and glucose transporter type 2 (GLUT2); elevation of glucose storage in the liver by enhancement of glucokinase; inhibition of  $\alpha$ -glucosidase and increasing adiponectin, leading to improvement in insulin resistance; and alleviation of ferroptosis (40-43). The results of the above studies might not match necessarily with the studies that carried on human, because these results investigated quercetin on animals.

In the present study, quercetin and gabapentin failed to decrease FSG. These results ascribed to the difficulties that faced Iraqi diabetic patients used insulin in general, and the 31 patients (77.5%) of this study that used insulin, in keeping the target glucose level when they used insulin because of most Iraqi people have an unhealthy eating habit, as well as sedentary lifestyle without exercises. This study showed that, quercetin is better than gabapentin in decreasing HbA1c despite insignificant p-value. The decrease that happened in group A ascribed to the effect of exogenous subcutaneous insulin and oral hypoglycemic drugs. Also, this clinical trial showed that, quercetin causes increase in insulin level insignificantly; and gabapentin failed to increase insulin blood level, instead, a decreased insulin blood level was obtained. These results distorted by different types and doses of exogenous insulin that used by the 31 patients (77.5%) of this study whose used insulin, but generally showed the effect of quercetin in increasing insulin secretion from  $\beta$ -cells. The actual index for the secretion of endogenous insulin is C-peptide level, and its level not altered by exogenous subcutaneous insulin at all (44,45). The present study showed that, quercetin causes a significant increase in C-peptide level. The decrease in C-peptide level that happened in group A ascribed to the effect of oral hypoglycemic drugs. Finally, these results indicate that, quercetin is better than gabapentin alone group in increasing insulin secretion because of the highest significant C-peptide level; in addition to a small degree in improving insulin sensitivity, as outlined by the mechanisms mentioned above.

There are no regression correlations in gabapentin alone group among Norfolk QOL-DN and versus glycemic control parameters. While, in quercetin group, the increase in C-peptide level correlates in a strong positive relationship with worsening Norfolk quality of life for diabetic neuropathy. In gabapentin alone group, the increase in BMI correlates in a strong positive relationship with worsening Norfolk quality of life for diabetic neuropathy; while female

gender associates moderately with worsening Norfolk quality of life for diabetic neuropathy. In quercetin group, the increase in age correlates in a very strong negative relationship with improving Norfolk quality of life for diabetic neuropathy; while in the same group, all female gender, illiterate and primary school, and low and somewhat moderate-income associate strongly with worsening Norfolk quality of life for diabetic neuropathy. In both of gabapentin alone and in quercetin group, there were no regression correlations found among Norfolk QOL-DN versus some disease characteristics.

This present novel study is the first study that find the regression correlations among Norfolk QOL-DN vs. glycemic control parameters after adding quercetin to gabapentin in treating patients with diabetic neuropathy. On searching on PubMed, The Cochrane Library, and MEDLINE, there is no study investigate the mentioned effects; so, there are no results that could compare with the results of this novel study. The current novel pioneer study prompts the researchers to investigate these subjects clinically more and more.

## 5. Conclusion

Adding quercetin is slightly better than dispensing gabapentin alone in relating to total Norfolk QOL-DN. Adding quercetin is very slightly better than dispensing gabapentin alone in relating to both of physical functioning/large fibers neuropathy domain and small fibers neuropathy domain. Some superiority of adding quercetin despite the insignificant p-value among the two groups in relating to all of activities of daily living (ADLs) domain, symptoms domain and autonomic neuropathy domain. So, adding quercetin to patients with DN has a slightly improving effect on Norfolk QOL-DN.

Quercetin is better in increasing insulin secretion due to the highest significant C-peptide level; beside a small degree in improving insulin sensitivity. The regression correlations that were found in quercetin group are increasing C-peptide level correlate in a strong positive relationship with worsening Norfolk QOL-DN, increasing age correlate in a very strong negative relationship with improving Norfolk QOL-DN, and all of female gender, illiterate and primary school, and low and somewhat moderate-income associate strongly with worsening Norfolk QOL-DN.

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