CASE STUDY

Effect of Adding Taurine to Gabapentin on Toronto Clinical Neuropathy Score in Patient with Diabetic Neuropathy

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ABSTRACT

Diabetic neuropathy is a type of nerve damage that can occur in patients with diabetes mellitus. High blood glucose can injure nerves throughout the body. Diabetic neuropathy most often damages nerves in the legs and feet causing symptoms like pain and numbness. Taurine has been widely investigated regarding to its properties as a neuroprotective agent, antioxidant, anti-inflammatory in several neurodegenerative diseases. 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 taurine 1 g thrice daily for 3 consecutive months. Adding taurine in combination with gabapentin significantly improves numbness, tingling, and temperature when compared with gabapentin alone. As well as, has a highly significant improving on ataxia. Taurine is better in improving insulin sensitivity due to lowering HbA1c level significantly, beside a medium degree in increasing insulin secretion; as evidenced by decreased fasting serum glucose, decreased HbA1c significantly, increased insulin level significantly, and increased C-peptide level. The conclusion of this study, adding taurine to patients with diabetic neuropathy has a significant improving effect on Toronto clinical neuropathy score by alleviating signs and symptoms, and improving insulin sensitivity.

Keywords: Diabetic neuropathy, Toronto clinical neuropathy score, Taurine.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic condition characterized by chronic hyperglycemia resulting from deficiency of insulin, or decreased insulin sensitivity, or both, in addition to interplay of environmental and genetic factors.[1] Chronic hyperglycemia and genetic predisposition eventually affect the microvasculature, which are leading to complications mainly from the eye, the kidneys and the nervous system.[2] One of the most common microvascular complication of DM is diabetic neuropathy (DN), which is usually undertreated and underdiagnosed in clinical practice.[3]

Oxidative stress in conjunction with hyperglycemia is known to activate many pathways such as polyol pathway, hexosamine flux, advanced glycation end products (AGEs), poly (ADP ribose) polymerase, mitogen-activated protein kinases, cyclooxygenase 2 activation, and altered activity of Na^+/K^+-ATPase which promote neuronal abnormalities and nerve damage.[4,5] Oxidative stress plays a major role in neuropathic pain etiology. Superoxide anions are the key mediators for the oxidative injury induced by glucose resulting in diabetic neuropathy.[6] Oxygen-free radicals interfere with the biologic function of neuronal cells via damage to the DNA, lipids and proteins, with the subsequent programming of neuronal cell death.[7] Compounds with antioxidant activity are potential candidates for the prevention of the complications associated with diabetes.[6]

Gabapentin given at a daily doses ranging from 1800 to 3600 mg provided a substantial or moderate pain relief in some patients with DN.[8] Due to its safety profile, gabapentin is extensively used off-label for variety of conditions.[9] Taurine has been widely investigated regarding to its properties as an anti-oxidant, anti-inflammatory, neuroprotective agent in several neurodegenerative diseases.[10] Animal studies have shown that supplementation of taurine provides beneficial effects in models of neurologic disease.[11] In human, taurine improves diabetes by exerting anti-inflammatory effects.[12]

The aim of this study is to evaluate for the first time the effects of taurine as adjuvant therapy with gabapentin in

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patients with diabetic neuropathy on the followings; Toronto clinical neuropathy scoring (TCNS) by alleviating symptoms and sings, glycemic control, and finding the statistical correlations among the main parameters.

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. Patients who were visited the center with diabetes were approached and those with mild to moderate diabetic neuropathy were selected. Patients were fully informed of the study protocol and written consent was obtained from all the participants before starting the study. The ethical and scientific committee of the Baghdad Al-Russafa Health Directorate approved the study. The study sample consisted of 40 participants enrolled randomly, then subdivided into two groups. Patients were included in the study according to the following criteria: (1) diabetic patients type 2 aged 30 to 65 years old, (2) patients with mild to moderate diabetic neuropathy. Patients were excluded according to the following criteria: (1) patients with type 1 diabetes mellitus, (2) patients with severe diabetic neuropathy, (3) patients with endocrine or gynecological diseases, (4) patients hypersensitive to any drug or supplement used in this study, (5) pregnancy and breastfeeding. They were categorized 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 taurine 1 g thrice daily for 3 consecutive months.

The TCNS Consists of Three Parts[13,14]

- Symptom scores: foot pain (burning and stabbing or electric-like shock), numbness (loss of sensation), tingling (paresthesia and dysesthesia), weakness (in the feet), ataxia (unsteadiness, balance when walking and standing), and upper-limb symptoms (symptoms in the hands: pain, numbness and tingling).
- Reflex scores: bilateral knee reflexes, bilateral ankle reflexes, bilateral biceps reflexes and bilateral triceps reflexes.
- Sensory test scores (physical examination scores): pinprick (by a pin-like neurotip from the neurological 4-piece diagnostic set; in diabetic neuropathy the patient cannot feel ≥ 1 touches on either toe or ≥ 2 on one toe), temperature (by a cold metal from the neurological diagnostic set because the thermo rollers are unavailable), light touch (pressure sensation by 10 g diabetic monofilament at 5 points in each foot; in diabetic neuropathy the patient feels fewer than 8 out of 10 touches), vibration sense (by 128 Hz tuning fork), position sense (by moving the toes while the patient closes his eyes).

The score ranges from a minimum of 0 (no neuropathy) to a maximum of 19 points. Diabetic neuropathy severity is graded as: 0–5 = no or minimal neuropathy; 6–8 = mild neuropathy; 9–11 = moderate neuropathy; and ≥ 12 = severe neuropathy. The TCNS has been employed in people with type 2 diabetes to assess the prevalence of painful distal symmetrical polyneuropathy (DSPN). If the score is from 6 to 11 points, then the patient had received a therapeutic course and followed up for three consecutive months (90 days).

In 10 mL of venous blood was withdrawn after 8 hours fasting from each patient at baseline before starting treatment and after 90 days at end of treatment by using 10 mL syringe. In 3 mL of the withdrawn blood was transferred to EDTA tube (1.5 mg/mL) and stored in a refrigerator at +2 to +8°C for analysis of HbA1c within 1 week. While 7 mL of the withdrawn blood was transferred to gel tube and leaved a while for clotting then centrifuged at speed of 3000 rpm for 15 minutes to separate serum. Serum samples were divided in an Eppendorf tube by micropipette and kept frozen at –20°C until the end of the study to measure the required parameters.

Data were analyzed using the SPSS software (version 28.0, Chicago, Illinois, USA). Also, data were subjected to Shairo test to check its normal distribution.

RESULTS

Demographic characteristics and socioeconomic status were presented in Table 1. There were no statistically significant differences between the study groups in values relating to age, gender, body mass index (BMI) (kg/m^2), waist circumference, blood groups, educational level, monthly income, smoking, and alcohol drinking.

Disease characteristics were presented in Table 2. There were no statistically significant differences between the study groups in values relating to duration of DM (years), duration of DN (years), family history of DM, family history of DN, medications used, presence of comorbidity(s), and number of comorbidities.

The effect of treatment on TCNS were presented in Table 3, which revealed a significant improvement ($p < 0.05$) in group B in relating to numbness at the end of treatment courses. Moreover, there was a significant improvement ($p < 0.05$) in group B in relating to tingling after finishing the treatment courses. In addition, there was a significant improvement ($p < 0.05$) in both A and B groups in relating to weakness after finishing the treatment courses. As well as, there was a significant improvement ($p < 0.05$) in group A in relating to ataxia. Also, group B improved significantly ($p < 0.01$) after finishing the treatment courses. Moreover, there was a significant improvement ($p < 0.05$) in group B in relating to temperature after finishing the treatment courses.

Table 4 revealed the effect of treatment on TCNS as a total score. There was a highly significant improvement ($p < 0.01$) in the two groups after finishing 3 months of treatment courses.

Table 5 shows the effect of treatment on glycemic control. There was a significant difference ($p < 0.05$) between the study groups in values of fasting serum glucose (FSG) of post-treatment. Moreover, a significant increase ($p < 0.05$) in FSG values in group A after 3 months of treatment. In addition, there was a highly significant decrease ($p < 0.01$) in values of

glycated hemoglobin (HbA1c) in group B after 3 months of treatment. As well as, a highly significant difference ($p < 0.01$) between the study groups in values of insulin was found only after finishing the treatment courses. Moreover, a significant increase ($p < 0.05$) in insulin values in group B after 3 months of treatment was found.

No significant correlations were reported among TCNS and glycemic control parameters for group A. There were strong positive relationships among TCNS with all of age, BMI, and waist circumference (WCF) for group A, where the correlation is significant at the 0.05 level (2-tailed). There were strong positive relationships among Toronto clinical neuropathy score with both DM and DN duration for group A. In addition, there was a medium association between TCNS and family history of DM, as presented in Table 6.

However, there were strong positive relationships among Toronto clinical neuropathy score with both of FSG and HbA1c, where the correlation is significant at the 0.05 level (2-tailed). There was a strong negative relationship between Toronto's clinical neuropathy score and age for group B. Nevertheless, there was a medium association between TCNS and educational level. In addition, there was a strong association between TCNS and income. However, there were insignificant correlations among TCNS vs. some disease characteristics, as presented in Table 7.

Table 1: Demographic characteristics and socioeconomic status

Demographic characteror socioeconomic statusN (%) N (%)			*Group A*	*Group B*	*p-value*
Age (years)	≤ 50		8 (20.0)	6 (15.0)	0.507 NS
	> 50		12 (30.0)	14 (35.0)	
Gender	Male		10 (25.0)	11 (27.5)	0.751 NS b
	Female		10 (25.0)	9 (22.5)	
BMI (kg/m2)	≤ 18.4		1 (2.5)	0 (0.0)	0.301 NS [a]
	18.5–24.9		10 (25.0)	5 (12.5)	
	25–29.9		4 (10.0)	9 (22.5)	
	≥ 30		5 (12.5)	6 (15.0)	
Waist circumference (cm)	Male	< 102	9 (22.5)	5 (12.5)	0.128 NS [a]
		≥ 102	1 (2.5)	7 (17.5)	
	Female	< 88	1 (2.5)	0 (0.0)	
		≥ 88	9 (22.5)	8 (20.0)	
Blood group	Rh+	A	2 (5.0)	5 (12.5)	0.466 NS [a]
		B	5 (12.5)	3 (7.5)	
		AB	2 (5.0)	5 (12.5)	
		O	10 (25.0)	7 (17.5)	
	Rh-	A	1 (2.5)	0 (0.0)	
Educational level	Illiterate		4 (10.0)	0 (0.0)	0.435 NS [a]
	Primary		8 (20.0)	8 (20.0)	
	Secondary		6 (10)	8 (20.0)	
	College		2 (5.0)	4 (10.0)	
Monthly income (dollars)	< $ 500		11 (27.5)	5 (12.5)	0.131 NS [a]
	$500–1000		7 (17.5)	10 (25.0)	
	> $1000		2 (5.0)	5 (12.5)	
Smoking	Yes		4 (10.0)	5 (12.5)	0.705 NS [a]
Alcohol drinking	Yes		1(2.5)	0 (0.0)	1.000 NS [a]

Data presented as (N): Number of patients, (%) Percentage. [a]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^2: kilogram per square meter, cm: centimeter, Rh: Rhesus factor.

DISCUSSION

Modified Toronto clinical neuropathy score (mTCNS) differs from TCNS in lack of reflex scores (which are not improved absolutely in this study) but has more details in determining both of symptoms and sensory test scores with a maximum of 33 points.[13] Numerous studies have confirmed the reliability and validity of mTCNS and TCNS in the diagnosis of diabetic

Table 2: Disease characteristics

Disease character N (%)		*Group A*	*Group B*	*p-value*
		N (%)		
Duration of DM (years)	< 1	0 (0.0)	0 (0.0)	0.350 NS [a]
	1–≤ 5	5 (12.5)	1 (2.5)	
	> 5–10	4 (10.0)	4 (10.0)	
	> 10	11 (27.5)	15 (37.5)	
Duration of DN (years)	< 1	3 (7.5)	4 (10.0)	0.949 NS [a]
	1 –≤ 5	14 (35.0)	13 (32.5)	
	> 5 – 10	3 (7.5)	2 (5.0)	
	> 10	0 (0)	1 (2.5)	
Family history of DM	Yes	17 (42.5)	18 (20.0)	0.632 NS [a]
	No	3 (7.5)	2 (5.0)	
Family history of DN	Yes	10 (25.0)	12 (30.0)	0.525 NS b
	No	10 (25.0)	8 (20.0)	
Medications used	OHA	3 (7.5)	5 (12.5)	0.429 NS [a]
	OHA insulin	17 (42.5)	15 (37.5)	
Presence of comorbidity(s)	Yes	13 (32.5)	8 (20.0)	0.113 NS b
	No	7 (17.5)	12 (30.0)	
Number of comorbidities (Mean ± SD)		1.5 ± 0.7	1.8 ± 1.2	0.071NS c

Data presented as (N): Number of patients, (%) Percentage. [a] 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.

Table 3: Effect of treatment on each score of TCNS

Score		*Patient Groups*		*p-value*
		Group A	*Group B*	
		N (%)	*N (%)*	
Foot pain	Pre	20 (50)	20 (50)	NA NS
	Post	20 (50)	19 (47.5)	1.000 NS [a]
p-value[c]		1.000 NS	0.500 NS	
Numbness	Pre	15 (37.5)	16 (40)	0.705 NS [a]
	Post	11 (27.5)	10 (25)	0.751 NS b
p-value[c]		0.125 NS	0.031*	
Tingling	Pre	17 (42.5)	19 (47.5)	0.605 NS [a]
	Post	16 (40)	11 (27.5)	0.176 NS [a]
p-value[c]		1.000 NS	0.008*	
Weakness	Pre	16 (40)	16 (40)	1.000 NS [a]
	Post	9 (22.5)	9 (22.5)	1.000 NS [a]
p-value[c]		0.016*	0.016*	
Ataxia	Pre	16 (40)	15 (37.5)	1.000 NS [a]
	Post	9 (22.5)	4 (10)	0.176 NS [a]
p-value[c]		0.016*	< 0.001**	
Upper limb symptoms	Pre	17 (42.5)	11 (27.5)	0.082 NS [a]
	Post	13 (32.5)	7 (17.5)	0.057 NS b
p-value[c]		0.125 NS	0.125 NS	
Bilateral knee reflexes	Pre	16 (40)	16 (40)	1.000 NS
	Post	16 (40)	16 (40)	1.000 NS
p-value[c]		1.000 NS	1.000 NS	
Bilateral ankle reflexes	Pre	13 (32.5)	12 (30)	0.702 NS [a]
	Post	13 (32.5)	12 (30)	0.702 NS [a]
p-value[c]		1.000 NS	1.000 NS	
Bilateral biceps reflexes	Pre	20 (50)	20 (50)	NA NS
	Post	20 (50)	20 (50)	NA NS
p-value[c]		1.000 NS	1.000 NS	
Bilateral triceps reflexes	Pre	20 (50)	20 (50)	NA NS
	Post	20 (50)	20 (50)	NA NS
p-value[c]		1.000 NS	1.000 NS	
Pin prick	Pre	20 (50)	19 (47.5)	1.000 NS [a]
	Post	19 (47.5)	18 (45)	1.000 NS [a]
p-value[c]		1.000 NS	1.000 NS	
Temperature	Pre	12 (30)	14 (35)	0.507 NS b
	Post	7 (17.5)	8 (20)	0.744 NS b
p-value[c]		0.063 NS	0.031*	
Light touch	Pre	18 (45)	18 (45)	1.000 NS [a]
	Post	18 (45)	19 (47.5)	1.000 NS [a]
p-value[c]		1.000 NS	1.000 NS	
Vibration sense	Pre	6 (15)	5 (12.5)	0.723 NS b
	Post	6 (15)	5 (12.5)	0.723 NS b
p-value[c]		1.000 NS	1.000 NS	
Position sense	Pre	2 (5)	1 (2.5)	1.000 NS [a]
	Post	1 (2.5)	0 (0)	1.000 NS [a]
p-value[c]		1.000 NS	1.000 NS	

Data presented as (N): Number, (%) Percentage. [a] Fisher's Exact test used to assess differences of parameters between groups, [b] Chi square test to assess differences in categorical variables, [c] McNamar test or marginal homogeneity test is used for comparing paired. NS: No significant changes (p≥0.05), * Significant changes(p<0.05), ** highly significant changes (p<0.01). NA: not applicable.

Table 4: Effect of treatment on TCNS

Total scoring Group A M (± SD)		*Patient Groups*		*p-value*[a]
		Group B		
		M (±SD)		
Toronto clinical neuropathy scoring	Pre	8.6 (±1.7)	8.3 (±1.8)	0.293 NS
	Post	7.1 (± 2.0)	6.1 (±1.9)	0.056 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≥0.05), ** highly significant changes (p<0.01).

Table 5: Effect of treatment on glycemic control.

Parameter M (±SD)		*Group A*	*Group B*	*p-value*[a]
		M (±SD)		
FBG (mmol/L)	Pre	12.32 (± 5.03)	13.18 (± 3.4)	0.265 NS
	Post	16.03 (± 5.52)	11.99 (± 5.21)	0.010 *
p-value[b]		0.024*	0.235 NS	
HbA1c (%)	Pre	9.74 (± 2.12)	10.66 (± 2.64)	0.117 NS
	Post	9.39 (± 2.1)	9.34 (± 2.51)	0.469 NS
p-value[b]		0.497 NS	< 0.001**	
Insulin (µIU/L)	Pre	13.2 (± 5.22)	14.68 (± 4.9)	0.186 NS
	Post	12.48 (± 4.86)	22.03 (± 10.29)	< 0.001**
p-value[b]		0.637 NS	0.003*	
C-peptide (ng/mL)	Pre	2.86 (± 1.04)	3.42 (± 1.22)	0.083 NS
	Post	3.44 (± 1.57)	3.98 (± 1.21)	0.111 NS
p-value[b]		0.130 NS	0.066 NS	

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≥0.05), * significant changes (p<0.05), ** highly significant changes (p<0.01). FSG: fasting serum glucose, HbA1c: glycated hemoglobin.

peripheral neuropathy with high sensitivity and specificity and with priority for mTCNS.[15,18] Unfortunately, mTCNS is difficult to applied on low educated patients, so, TCNS was applied in the diagnosis, which is more applicable and

Table 6: Correlations among Toronto clinical neuropathy score vs. glycemic control parameters, demographic data and disease characteristics for group A.

Part I					
p-value & R		FBG a	HbA1c a	Insulin a	C-peptide a
TCNS	Correlation Coefficient (R)	-0.133	0.042	-0.397	-0.172
	P-value	0.288	0.430	0.042	0.234

Part II							
p-value & R		Age a	BMI a	WCF a	Gender b	Educational level b	Income b
TCNS	Correlation Coefficient (R)	0.469*	0.461*	0.417*	0.365	0.290	0.136
	P-value	0.018	0.020	0.034	0.057	0.107	0.283

Part III						
p-value & R		Duration of DM a	Duration of DN a	Family history of DM b	Family history of DN b	Number of comorbidities a
TCNS	Correlation Coefficient (R)	0.474*	0.527*	0.512*	0.364	-0.204
	p-value	0.017	0.008	0.010	0.057	0.195

[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, DM: diabetes mellitus, DN: diabetic neuropathy, FSG: fasting serum glucose, HbA1c: glycated hemoglobin, TCNS: Toronto clinical neuropathy score, WCF: waist circumference.

Table 7: Correlations among Toronto clinical neuropathy score vs. glycemic control parameters, demographic data and disease characteristics for group B.

Part I					
p-value & R		FBG [a]	HbA1c [a]	Insulin [a]	C-peptide [a]
TCNS	Correlation Coefficient (R)	0.407*	0.480*	0.001	-0.314
	p-value	0.037	0.016	0.498	0.089

Part II							
p-value & R		Age a	BMI a	WCF a	Gender b	Educational level b	Income b
TCNS	Correlation Coefficient (R)	-0.447*	-0.093	0.107	0.114	0.475*	0.662**
	p-value	0.024	0.349	0.326	0.316	0.017	<0.001

Part III						
p-value & R		Duration of DM [a]	Duration of DN [a]	Family history of DM [b]	Family history of DN [b]	Number of comorbidities [a]
TCNS	Correlation Coefficient (R)	0.080	-0.142	0.199	1.000	-0.059
	p-value	0.736	0.551	0.400	0.676	0.804

[a] Pearson's r correlation & simple linear regression used for the grouped data to findCorrelation 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). ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). BMI: body mass index, DM: diabetes mellitus, DN: diabetic neuropathy, FSG: fasting serum glucose, HbA1c: glycated hemoglobin, TCNS: Toronto clinical neuropathy score, WCF: waist circumference.

appropriate for Iraqi patients in general, where the symptoms in the score system are either absent or present.

When searching on PubMed, The Cochrane Library, and MEDLINE, famous medical research websites, no study investigates the effect of taurine or quercetin on Toronto clinical neuropathy score. The current novel study is the first study that investigates these effects. Taurine in combination with gabapentin, significantly improves numbness, tingling, and temperature when compared with gabapentin alone. As well as, has a highly significant improving effect on ataxia. However, the significant improving effect on weakness is as same as to that of gabapentin alone. Despite the insignificant

effect of taurine plus gabapentin on foot pain, the *p-values* is lower than that of gabapentin alone because of one patient had improved. In contrast, the *p-values* are the same for the two groups regarding the remaining insignificant scores. In spite of the significant improving effect of the two groups on the total score, taurine has much lower effect on the total score of TCNS. Several studies have reported that increased HbA1c variability and FSG levels are associated with an increased risk of DPN in patients with T2DM.[19-21] Some studies have revealed that taurine plasma concentrations are decreased in T1DM and T2DM patients and in women with gestational diabetes.[22,23] A study has linked between taurine deficiency and the development of most of diabetic complications in human.[22] Taurine exerts its effects on glucose homeostasis through two mechanisms: by its effects on β-cell insulin secretion and interfering with the insulin receptor (IR) signaling pathway and post-receptor intracellular events.[23,24]

In β-cells, taurine exerts antidiabetic activity by increasing insulin secretion via the following mechanisms: it regulates adequate glucose transporter-2 (GLUT-2) gene expression via V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MAf-A) and pancreatic and duodenal homeobox (PDX-1); improves ATP-sensitive K^+ (K_{ATP}) channels inhibition, leading to better β-cell depolarization action; increases protein content of voltage-sensitive calcium channels, ameliorating calcium influx; and enhances calcium influx to mitochondria, resulting in supporting oxidative metabolism. The increase in intracellular calcium concentration [Ca^{2+}] may activate adenylyl cyclase (AC), which then increases cyclic adenosine monophosphate (cAMP) cellular concentration, leading to protein kinase-A (PKA) catalytic subunit released from the regulatory subunit; PKA phosphorylates the calcium channels, and enhancing its voltage activity and sensitivity; finally, PKA together with calcium regulates insulin granule exocytosis.[23-27]

When interfering with IR, taurine decreases blood glucose level via the following mechanisms; it decreases hepatic glucagon action and enhances hepatic insulin receptor-β/protein kinase B (IRβ/Akt) activation, which favors glycolysis and glycogen biosynthesis, and suppresses glycogenolysis and gluconeogenesis, leading to reduction in hepatic glucose output.[23,28] Most of the above studies investigated the effects of taurine on animals and their results might not match necessarily with the clinical trials that carried on human beings.

In the present study, taurine decreased fasting serum glucose. These results ascribed to the difficulties that faced Iraqi diabetic patients used insulin in general, and the 32 patients (80%) of this study that used insulin, in suffering from maintaining target glucose level when used insulin due to the unhealthy eating habits of most Iraqi people, as well as sedentary lifestyle. Despite that, this study confirmed decreased FSG by taurine. This study showed that, taurine decreased HbA1c significantly, which corresponded somewhat with decreased FSG. Also, this study showed that, taurine increased insulin level significantly; gabapentin failed to increased insulin level, actually a decreased insulin level was obtained. These results were distorted by different types and doses of exogenous insulin used by the 32 patients (80%) of this study whose used insulin, but in general showed the effect of taurine in increasing insulin secretion. C-peptide level is the actual index for endogenous insulin secretion, and its level is not distorted by exogenous insulin.[29] This study showed that, taurine increased the C-peptide level more than gabapentin alone group despite an insignificant p-value. The decrease that happened in group of gabapentin alone was ascribed to the effect of OHA. Furthermore, these results indicate that, taurine is better in improving insulin sensitivity due to lowering HbA1c level significantly, besides a medium degree in increasing insulin secretion.

Group A has no regression correlations among TCNS vs. glycemic control parameters. However, in the taurine group, increasing both FSG and HbA1c correlates in a strong positive relationship with worsening TCNS. In group A, increasing all of age, BMI and WCF correlate in a strong positive relationship with worsening TCNS. In the taurine group, increasing age correlates in a strong negative relationship with enhancing TCNS. Moreover, primary school educational level and low income (<$500) associate moderately and strongly with worsening TCNS. In group A, increasing both durations of DM and DN correlate in a strong positive relationship with worsening TCNS; a negative family history of DM is associated moderately with worsening TCNS. There were no regression correlations among TCNS *vs*. some disease characteristics in the taurine group.

The present novel study is the first study that find the regression correlations among TCNS and glycemic control parameters after adding taurine to gabapentin in treating patients with diabetic neuropathy in Iraq. On searching on medical websites, there is no study investigating the mentioned effects, so, there are no results that could compare with the results of this study. The current novel pioneer study prompts the researchers to investigate these subjects clinically more and more.

CONCLUSION

In spite of the significant improving effect of the two groups on the total score, taurine has much lower effect on the total score of TCNS. Adding taurine in combination with gabapentin significantly improves numbness, tingling, and temperature when compared with gabapentin alone. As well as, has a highly significant improving effect on ataxia. So, adding taurine to patients with DN significantly improves TCNS by alleviating symptoms and signs.

Taurine is better in improving insulin sensitivity due to lowering HbA1c level significantly, beside a medium degree in increasing insulin secretion, as evidenced by decreased fasting serum glucose, decreased HbA1c significantly, increased insulin level significantly, and increased C-peptide level.

The regression correlations that were found in the taurine group are increasing both of FSG and HbA1c correlate in a

strong positive relationship with worsening TCNS, increasing age correlates in a strong negative relationship with enhancing TCNS, and primary school educational level and low income (<$500) associate moderately and strongly with worsening TCNS respectively.

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