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Physicians' Perception and Practice of Prescribing Vitamin B Combination Versus Antiepileptic Drugs for Diabetic Neuropathy: Content Validity, Reliability and Pilot Study

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Abstract

Diabetic neuropathy (DN) is the most common complication of diabetes mellitus causing increased morbidity and mortality. Although international guidelines did not include vitamins and dietary supplements in any line of management, these agents were prescribed by a significant number of physicians either as preventive or treatment of DN. This study aimed to develop a validated questionnaire that examines the physicians' perception and practice towards prescribing vitamins or dietary supplements for DN treatment. The questionnaire was developed upon literature review via PubMed, Medline, Web of Science, Scopus, and Google Scholar. The questionnaire was revised upon experts' views and opinions. The constructed questionnaire was validated by the means of content validity and internal consistency. Finally, the developed questionnaire was piloted in a small representative sample of the original future aimed research target population, to test its applicability and feasibility. A total of 22 items questionnaire were developed in two domains (knowledge and perception domain and practice domain). Content validity analysis results met a satisfactory level, in which the S-CVI/UA value was 0.86 for both clarity and relevance. The questionnaire also showed good reliability, in which the Cronbach's alphas was 0.805. In conclusion, this study showed the that constructed questionnaire had a good level of validity (content validity) and reliability that is able to cover different aspects of the current state of perception and practice among physicians regarding the management of DN. The preliminary results of the pilot study showed a good knowledge and perception of the respondents with DN. Even in the absence of a local guideline, the respondents followed the international guidelines in choosing anti-neuropathic agents however, they tended to add vitamin B complex/B_{12} as an adjuvant in their management plan.

Keywords: Diabetic neuropathy, neurotrophic B vitamins, physician, vitamins.

تصور الأطباء وممارستهم في وصف مزيج فيتامين ب مقابل الأدوية المضادة للصرع لاعتلال الاعصاب السكري: صحة المحتوى والموثوقية والدراسة التجريبية

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الخلاصة

اعتلال الأعصاب السكري هو أكثر المضاعفات شيوعًا لمرض السكري مما يؤدي إلى زيادة معدلات المرض والوفيات. على الرغم من أن الدلائل الإرشادية الدولية لم تتضمن الفيتامينات والمكملات الغذائية في أي خط من خطوط العلاج، الا انه يتم وصف هذه المكملات الغذائية والفيتامينات من قبل عدد كبير من الأطباء إما كوقاية او علاج لمرضى اعتلال الاعصاب السكري. هدفت هذه الدراسة إلى تطوير استبيان ثم التحقق منه لفحص تصور الأطباء وممارستهم تجاه وصف الفيتامينات أو المكملات الغذائية لعلاج اعتلال الاعصاب السكري. تم تطوير الاستبيان بناءً على مراجعة الأدبيات عبر PubMed وMedline وWeb of Science وScopus وGoogle Scholar. تم تنقيح الاستبيان بناء على افكار الخبراء وآرائهم. تم التحقق من صحة الاستبيان الذي تم إنشاؤه من خلال صحة المحتوى والاتساق الداخلي. أخيرًا، تم تجريب الاستبيان المطور في عينة صغيرة تمثل المجتمع المستهدف للبحث في المستقبل، وذلك لاختبار قابليته للتطبيق وجدواه. تم تطوير ما مجموعه 22 فقرة استبيان في مجالي (الإدراك والممارسة). حققت نتائج تحليل صدق المحتوى مستوى مرضٍ، حيث كانت قيمة S-CVI / UA 0.86 للوضوح والملاءمة. أظهر الاستبيان أيضًا موثوقية جيدة، حيث كانت ألفا كرونباخ 0.805. أظهرت هذه الدراسة أن الاستبيان الذي تم إنشاؤه كان يتمتع بمستوى جيد من الصلاحية (صحة المحتوى) والموثوقية القادرة على تغطية الجوانب المختلفة للحالة الحالية للإدراك والممارسة بين الأطباء فيما يتعلق بعلاج مرض اعتلال الاعصاب السكري. أظهرت النتائج الأولية للدراسة التجريبية معرفة جيدة وتصور المستجيبين الذين يعانون من مرض اعتلال الاعصاب السكري. حتى في حالة عدم وجود بروتوكولات علاجية محلية، اتبع المشاركون البروتوكولات الدولية في اختيار الادوية المناسبة لعلاج مرض اعتلال الاعصاب السكري ومع ذلك، فإنهم يميلون إلى إضافة فيتامين ب المركب / ب ١٢ كعامل مساعد في الخطة العلاجية.

الكلمات المفتاحية: اعتلال الأعصاب السكري ، فيتامينات ب المقوية للاعصاب ، طبيب ، فيتامينات.

Introduction

Diabetes mellitus is defined as a metabolic disorder caused by multifactorial aetiologies and presented by chronic hyperglycemia with defects in carbohydrate, fat, and protein metabolism resulted from either abnormal insulin secretion, insulin action or both [(1)]. In 2021, the International Diabetes Federation stated that there are about 537

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million diabetes cases, and this number is projected to reach 643 million by 2030, and 783 million by 2045 [2]. The rapid escalation in the number of cases will be accompanied by a direct increase in the prevalence of the chronic complications of the disease [3].

Diabetic neuropathy (DN) is the most common complication of diabetes mellitus [4] causing increased morbidity and mortality [5] furthermore causing a great burden on health care expenditure [6]. DN is defined as a neurodegenerative disorder that affects the somatic and/ or autonomic peripheral nervous system in the setting of diabetes mellitus without other causes of neuropathy [7]. Despite its heavy burden on healthcare systems and the better understanding of the multifactorial pathogenesis of the disease, DN still underdiagnosed and undertreated [8]. In the absence of evidence-based disease-modifying pharmacological agents, the mainstay of the management is based on glucose control, lifestyle changes, and pain management [9]. Despite the relatively high prevalence of DN in Iraq [10], there is no local or regional guideline of DN management [11]. Neurotropic B vitamins (B1, B6 and B_{12}) were well-known to have a crucial role in maintaining healthy nervous system [12]. It was suggested that these vitamins may increase the availability and effectiveness of noradrenaline and 5-hydroxytryptamine in the descending inhibitory nociceptive system [13, 14] furthermore, in some countries they were classified as analegesic drugs [14].It was hypothesized that neurotropic B vitamins support directing the Wallerian degeneration process (which is an active process that commenced after a nerve injury of degeneration of an axon) toward regeneration and remyelination [15], several clinical trials conducted to highlight the effect of administration of the neurotropic B vitamins together with different dose regimes [16 - 18], however the positive outcomes was limited to improvement in symptoms of pain numbness and paraesthesia with no improvement in neurophysiological parameters. Thiamin (B1) had been shown to serve as a cofactor for three important enzymes that were involved in carbohydrate metabolism [19], in addition to have an important role in abolishing the metabolic dysregulations caused by high glucose level including polyol pathway, protein kinase C pathway, hexosamine pathway and increased advanced glycation end products which are the proposed mechanisms of DN pathogenesis [19, 20]. Benfotiamin which is a synthetic derivative of thiamin with better pharmacokinetic properties [21, 22] was shown to improve the Neuropathy Symptom Score in a double-blind randomized placebo-controlled phase III clinical study (BENDIP) [23]. Despite the fact that the association between vitamin B6 level and diabetes mellitus was well established [24], two clinical trials of pyridoxin administration in patients with DN were failed to improve subjective and objective parameters of the disease [25, 26]. Furthermore, concerns were raised about the safety profile of pyridoxin following several case reports about its possible toxic effects on nerves [27,28] which was proposed to be due to disruption of Gamma-Aminobutyric Acid (GABA) biosynthesis [29] which led several Food Safety Authorities is several countries to decrease the allowed upper limit of pyridoxin dose [30,31]. A long-term trial was showed a significant effect of metformin on B_{12} and methylmalonic acid (MMA) level with concurrent worsening of neuropathy symptoms [32]. Several clinical trials concluded a positive effect of methylcobalamin (active form of vitamin B_{12}) on the symptoms of DN with no effects on the nerve study parameters [33 - 35] until recently (2021) a prospective one-year, randomized double-blind, placebo-controlled trial, concluded positive effects of 1 mg methylcobalamin on in sural nerve conduction parameters along with Michigan Neuropathy Screening Instrument Questionnaire (MNSIq), the level of pain, and the quality of life [36]. Although the latest international guidelines did not include vitamins and dietary supplements in any line of management (e.g., the National Institute for Health and Care Excellence National (NICE) updated guideline in 2020 [37] and the American Diabetes Association (ADA) guideline in 2021[38]). A recent study, that was conducted in Saudi Arabia, found that a significant number of physicians were prescribing vitamin B_{12} either as preventive or treatment to their patients with DN [55]. The supplements have a heavy economic burden for patients in a developing country like Iraq, which lacks national health insurance programs. In addition to the fact that the safety profile of some heavily prescribed vitamins is questionable [39]. This study aimed to develop a validated questionnaire to assess physicians' perception and practice towards the prescribing of vitamins and dietary supplements versus pharmacological agents for the management of DN.

Methods

The study design involves three phases. In phase one, the construction of the first draft of the questionnaire from an interpretation of the literature on the research topic. In phase two, the content validity of the drafted questionnaire was tested to verify the applicability and appropriateness. Finally, in phase three, the internal consistency of the questionnaires was piloted to ensure reliability and feasibility.

Phase one

The literature review was conducted between the 1st of October 2021 and the 30th of December 2021 for published articles before the time of the research (no time limit was set to get as many as possible articles on the research topic). The search was only for full articles, written in English or Arabic languages that are examining healthcare

professionals' or physicians' knowledge, attitude, perception, and practice toward neuropathic pain treatment or management. The exclusion criteria were; articles written in languages other than English or Arabic, abstracts, articles examining patients' perspectives rather than physicians.

The literature review was conducted by the first author, a master student and the chief investigator, which were trained to search for relevant articles via the available databases and search engines including PubMed, Medline, Web of Science, Scopus, and Google Scholar. The Medical subject headings (MeSH) terms used in the search were supplied as a supplementary file.

The number of results retrieved from the literature review through the above-mentioned databases was 86 researches of a variety of formats. Following a screening of the retrieved researches and excluding irrelevant ones, the final number of researches chosen was 10 (Figure 1).

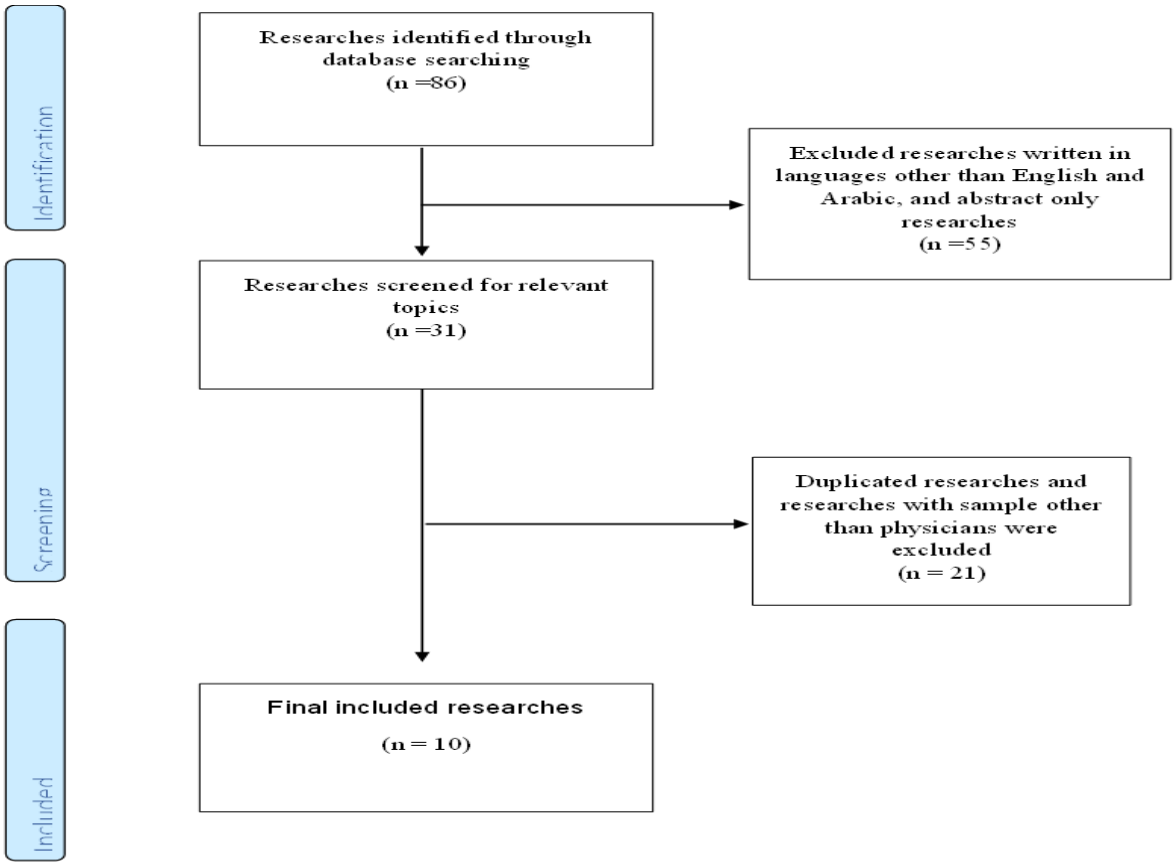

Figure 1. Workflow showing the process of literature review for constructing the first draft of the questionnaire

Based on the results of the literature review, the ten chosen articles were reviewed and used in the construction of the initial draft of the questionnaire. The questionnaire was constructed in English language since Iraqi physicians are more familiar with medical terminology in English rather than Arabic language. Then the questionnaire was sent independently to two experts in KAP (knowledge, attitude, and practice) tools at the University of Baghdad and the University of Duhok to verify the relevance and appropriateness of the questionnaires for the study topic. Based on the experts' views, the first draft was amended accordingly to improve the clarity and the structure of the questionnaire. This was followed by a second review process by another independent reviewer at the college of Pharmacy, University of Mosul to evaluate the questionnaire and eliminate redundancy and ambiguity, and to develop a final draft of the questionnaire. The questionnaire was developed to explore the physicians' perception and practice towards the prescribing of vitamins and dietary supplements versus pharmacological agents for the management of DN. Therefore, the items (questions) were allocated into two main domains (knowledge and perception domain and practice domain). The knowledge and perception domain aimed to closely examine the basic knowledge and the general perception of the physicians about DN (including the commonality of DN, its effect on patient's

quality of life, mortality rate and the difficulty of treatment in addition to the perception about dietary supplements and vitamin B). The practice domain aimed to explore the physicians' prescribing plans regarding anti-neuropathic agents and dietary supplements and indifferent cases. In addition to the factors that affect the choice of these agents. The time expected for completing the questionnaire (10 – 20 minutes) was enough for almost all of the respondents.

Content validity

The six steps of the content validity procedure were conducted as follow: (I) content validity form development, (II) assigning an expert review panel, (III) distributing the content validation form to the expert (d) reviewing the domain and items (e) setting a score to each item (f) determining the content validity index (CVI) (40). In which the CVI uses item-CVI (I-CVI) and scale-CVI (S-CVI) to report content validity in questionnaire development (41). The I-CVI is determined by dividing the total number of experts by the number of experts who rated each item on a scale of 'very relevant' (score 1), 'relevant' (score 1), 'irrelevant' (score 0), and 'very irrelevant' (scoring 0) (42). The I-CVI value range of 0.8 or more indicates that the item is relevant, however, if the value is less than 0.8 and more than 0.69, this would suggest item revision, while a value of less than 0.7 indicates an item to be eliminated. The sum of all items with I-CVI equal to 1 divided by the total number of items for the S-CVI yielded the universal agreement (UA) among experts (S-CVI/UA). A content validity index of S-CVI/UA 0.8 indicates outstanding content validity (43). Eight experts, including physicians and pharmacists from the University of Mosul and Ninevah University, as well as retired physicians, were recruited to judge the items using a scoring system ranging from 1 (the item is not relevant at all) to 4 (the item is highly relevant). If the items were scored lower than 3, in the comments, the experts were asked to offer a note or a suggestion to rephrase the item.

Reliability

Internal consistency is an indicator of a questionnaire's homogeneity (44). It reflects how close the questions (items) of a questionnaire are intercorrelated and hence measure the same concept. Cronbach's alpha (α) value is used as a measure of internal consistency (45). The internal consistency reliability of the two domains (knowledge and perception domain, and practice domain) was tested using Cronbach's alpha coefficient. Forty-five participants were enrolled to complete the questionnaire, the sample size was satisfying the Central Limit Theorem which assumed that the distributional assumption of the sample size of 30 or more to guarantee an equal mean between any sample and the target population (46).

Pilot study

To test the feasibility and usability of the questionnaire, a pilot study was conducted. A total of 45 physicians in different specialties were recruited. A convenience purposive sampling from Avicenna Hospital and Al-Quds primary health centre in Mosul, Iraq. Ethical approval was obtained from the Medical Research and Ethics Committee of the Department of clinical pharmacy, College of Pharmacy, University of Mosul. Ethical approval was also obtained from the Collegiate Committee for Medical Research Ethics at the University of Mosul (code: CCMRE-phA-22-2) to conduct the study. The physicians were contacted to participate in this pilot via telephone and verbal consent was given to participate in the study. On the day of the interview, written consent was given by the participants. The researcher discussed the aims of the research and handed the paper survey questionnaire. The questionnaires were filled out in 15 minutes (±3 minutes). The face-to-face data collection started from the 20th to the 31st of January 2022.

Statistical analysis

Data obtained from the respondents (for content validity, reliability and pilot study) were entered to Microsoft Excel (2016) software to calculate the content validity. Then the data was moved to the Statistical Package for the Social Sciences (SPSS) software version 24 to run the reliability test. Descriptive analyses (percentages and frequencies) were carried out using SPSS software for the pilot study.

Results

Phase one

The process of reviewing the literature via PubMed, Medline, Web of Science, Scopus, and Google Scholar databases resulted in 86 researches of a variety of formats (abstracts, posters, full articles, and books). These materials were screened by means of the titles and abstracts to remove duplicates and irrelevant articles. Ten full-text articles were retrieved for further evaluation based on the inclusion and exclusion criteria (Figure 1). The final number of researches chosen was 10 (Table 1).

Table 1. Literature review articles

Author	Country	Aim	Sample size	Participants ' profession	Method
Hall et al. (2006) [47]	UK	To report drug treatment of neuropathic pain as managed by UK primary care physicians.	686 primary care centers.	NA	Utilization analysis
Aakash et al.(2008) [48]	India	To inquire about their prescribing preferences among the drug options that were provided, to treat painful diabetic neuropathy	89	Physician	Survey
Possidente et al, (2009) [49]	UK	To evaluate provider practices for identification and treatment of painful diabetic peripheral neuropathy	357	Physician, Nurse, Nurse practitioner, Physician assistant, Others, Pharmacist	Survey
Benzon et al. (2013) [50]	US	To determine prescription patterns and whether these practices reflect current expert opinion.	474	Physician	Survey
Mabrouk et al, (2013) [51]	Egypt	To assess family physicians' knowledge, attitude, and practice regarding DN.	60	Physician	Survey
Lalonde et al. (2014) [52]	Canada	To evaluate and identify the determinants of the KAP of primary care physicians and pharmacists.	248	physician & pharmacist	Survey
Malik et al. (2017) [53]	Hong Kong, Malaysia, the Philippines, Taiwan, and Thailand	To examine the physician perceptions of painful DN and clinical practice behaviours in five countries in South-East Asia.	100	Physician	Survey
Provenzano et al, (2018) [54]	US	To assess the knowledge and practice of PCPs in the management of chronic pain	300	Primary care physicians	Survey
Aldossari et al, (2021) [55]	Saudi Arabia	To investigate local physicians' knowledge and tendency to prescribe vitamin B_{12} or vitamin B complex for the treatment or prevention of diabetic peripheral neuropathy.	412	Physician	Survey
Moon et al. (2021) [56]	Korea	To analyze the pharmacological treatments for DN.	NA	NA	Utilization analysis

The questionnaire was developed from the tools of the retrieved articles with modification to meet the aims of the developed questionnaire and to make it more suitable for the Iraqi healthcare system, which differs massively from other healthcare systems where other articles were conducted. The questions were allocated into two main domains, namely, the knowledge and perception domain, including eight items, and the practice domain including 16 items. The first draft of the questionnaire was reviewed by two experts; these include deletion of two questions for redundancy and irrelevance. The experts also requested to rephrase three more questions to improve the clarity of the questions. On the second round of review, an expert suggested adding a "not sure" for questions with an answer of "yes" or "no" for closed-ended questions. The final draft consisted of 22 items (seven items in knowledge and perception domain and fifteen items in the practice domain) (Table 2).

Table 2. Questionnaire's domains

Knowledge and perception domain		
Item 1	**Knowledge about DN**	**Response**
	DN is a common complication of diabetic patients	Agree, neutral, disagree
	DN affects patient's quality of life	Agree, neutral, disagree
	DN increases mortality rate	Agree, neutral, disagree
	DN is difficult to manage	Agree, neutral, disagree
	DN management plan is based on symptomatic relief	Agree, neutral, disagree
	DN can be reversed by strict blood glucose control	Agree, neutral, disagree
	DN incidence can be decreased by maintaining strict glucose control	Agree, neutral, disagree
Item 2	**Do you think that there is a definite treatment for DN?**	Yes, No, Not sure
Item 3	**Is there any local guideline for the management of diabetic neuropathy?**	Yes, No, Not sure
Item 4	**Knowledge about dietary supplements in DN**	
	Vitamins and dietary supplements are approved by the FDA	Agree, neutral, disagree
	Vitamins and dietary supplements' manufacturing undergoes quality control just like chemical medicines	Agree, neutral, disagree
	Vitamins and dietary supplements are safe on long term use	Agree, neutral, disagree
	Vitamins and dietary supplements have no side effects	Agree, neutral, disagree
	Vitamins and dietary supplements have no interactions with other medications	Agree, neutral, disagree
	The cost of vitamins and dietary supplement worth the efficacy (outcome) provided.	Agree, neutral, disagree
Item 5	**Knowledge about vitamin B complex/B_{12}**	
	Vitamin B complex/ B_{12} supplementation can prevent the development of DN	Agree, neutral, disagree
	Vitamin B complex/ B_{12} supplementation can treat DN	Agree, neutral, disagree
	Vitamin B complex/ B_{12} supplements are safe for long term use in treatment of DN	Agree, neutral, disagree
Item 6	**What is the most common cause of DN?**	Toxic effects of glucose, Oxidative stress, Vascular damage, Vitamin B_{12} deficiency
Item 7	**What is (are) the source of information does you follow in managing DN?**	Information from senior colleagues, Information from colleagues of different specialty, Internet and social media Reputable international guidelines, like American diabetes association (ADA), NICE, etc. Textbooks or scientific journals, Own practice
	Practice domain	***Response***
Item 1	**Do you recommend/ prescribe a dietary supplement to your patients with DN**	Yes No
Item 2	**If you answered to the previous question with Yes, how often do you recommend/ prescribe supplements to your patients with DN?**	Always Sometimes Rarely

Continued table (2)

Item 3	**Vitamins and dietary supplements in DN are usually prescribed by physicians as:**	Treatment (monotherapy), Adjuvant, Tonic only, prophylaxis, satisfy the patient (placebo)
Item 4	**The effectiveness of an agent is an important factor in choosing DN medication**	Agree, neutral, disagree
Item 5	**The safety of an agent is an important factor in choosing DN medication**	Agree, neutral, disagree
Item 6	**Patient preference is an important factor in choosing DN medication**	Agree, neutral, disagree
Item 7	**Drug - drug interaction is an important factor in choosing DN medication**	Agree, neutral, disagree
Item 8	**Cost of an agent is an important factor in choosing DN medication**	Agree, neutral, disagree
Item 9	**Patient factors including co-morbidity are important factors in choosing DN medication**	Agree, neutral, disagree
Item 10	**Medical advertisement of an agent is an important factor in choosing DN medication**	Agree, neutral, disagree
Item 11	**A 45 years old male diabetic patient (normal BMI and no comorbidities) is complaining of burning and tingling sensation pain in his feet especially at night, what is the drug of choice for this patient?**	Amitriptyline, Carbamazepine, Duloxetine, Gabapentin, Pregabalin, Vitamin B complex, Vitamin B_{12}
Item 12	**The extent of influences of international guidelines on your practice**	I never use them, I consult them occasionally, They are fundamental to my practice
Item 13	**Management plan of [Mild DN]**	Life style change (diet, exercise), Strict control on blood sugar, Supplements (vitamin B complex / Vit B_{12}, Anticonvulsants or TCA or SNRI, Combination of (anticonvulsant+ TCA and/or SSRI+ supplement)
Item 14	**Management plan of [Moderate DN]**	Life style change (diet, exercise), Strict control on blood sugar, Supplements (vitamin B complex or Vit B_{12},…etc), Anticonvulsants or TCA or SNRI, Combination of (anticonvulsant+ TCA and/or SSRI+ supplement)
Item 15	**Management plan of [Severe DN]**	Life style change (diet, exercise), Strict control on blood sugar, Supplements (vitamin B complex or Vit B_{12},…etc), Anticonvulsants or TCA or SNRI, Combination of (anticonvulsant+ TCA and/or SSRI+ supplement)

Phase two (content validity)

To determine the content validity of the preliminary version of the questionnaire, an expert panel of eight healthcare professionals was recruited. The experts rated the items' (questions') clarity and relevance on a scale from (1 - 4) to calculate the I-CVI, S-CVI, and S-CVI/UA. Tables 2 and 3 show the calculation of the validity indices for both clarity and relevance. The validity indices met satisfactory levels (Tables 3, 4 and 5).

Table 3. Calculations of the content validity for relevance

Item	Expert1	Expert2	Expert3	Expert4	Expert5	Expert6	Expert7	Expert8	Expert in agreement	I-CVI	UA
1	4	4	4	4	4	4	4	4	8	1	1
2	4	4	4	3	4	4	4	4	8	1	1
3	4	4	4	3	4	3	3	4	8	1	1
4	4	4	4	4	4	4	4	4	8	1	1
5	4	4	4	4	2	4	3	3	7	0.875	0
6	3	4	4	4	3	4	4	4	8	1	1
7	4	4	4	4	3	4	4	4	8	1	1
8	4	4	3	4	3	4	4	4	8	1	1
9	4	4	4	4	4	4	3	4	8	1	1
10	4	4	4	3	3	4	3	4	8	1	1
11	4	4	4	4	4	4	4	4	8	1	1
12	4	4	4	4	4	4	4	4	8	1	1
13	4	4	4	4	4	4	4	4	8	1	1
14	4	4	4	4	3	4	4	4	8	1	1
15	4	4	4	4	4	4	1	3	7	0.875	0
16	4	4	4	3	3	4	3	4	8	1	1
17	4	4	4	4	4	4	3	1	7	0.875	0
18	4	4	4	4	4	4	3	4	8	1	1
19	4	4	4	4	4	4	4	4	8	1	1
20	4	4	4	4	4	4	4	4	8	1	1
21	4	4	4	4	4	4	4	4	8	1	1
22	4	4	4	4	4	4	4	4	8	1	1

Table 4. Calculations of the content validity for Clarity

Item	Expert1	Expert2	Expert3	Expert4	Expert5	Expert6	Expert7	Expert8	Expert in agreement	I-CVI	UA
1	4	3	4	4	4	4	4	2	7	0.875	0
2	4	4	4	3	4	4	4	4	8	1	1
3	4	4	4	3	4	3	4	4	8	1	1
4	4	4	4	4	4	3	4	3	8	1	1
5	3	4	4	4	4	3	4	4	8	1	1
6	4	4	4	4	4	4	4	4	8	1	1
7	4	4	4	4	4	3	4	4	8	1	1
8	4	4	4	4	4	4	4	4	8	1	1
9	4	4	4	3	4	4	3	4	8	1	1
10	4	4	4	4	4	4	4	4	8	1	1
11	4	2	4	4	4	4	4	4	7	0.875	0
12	4	4	4	4	2	4	4	4	7	0.875	0
13	4	4	4	4	3	4	4	4	8	1	1
14	4	3	4	4	4	4	4	4	8	1	1
15	4	3	4	4	4	4	4	4	8	1	1

Continued table4.

16	4	3	4	4	4	4	4	4	8	1	1
17	4	4	4	3	4	3	4	4	8	1	1
18	4	4	4	4	4	3	4	3	8	1	1
19	3	4	4	4	4	3	4	4	8	1	1
20	4	4	4	4	4	4	4	4	8	1	1
21	4	4	4	4	4	3	4	4	8	1	1
22	4	4	4	4	4	4	4	4	8	1	1

Table 5. Validity indices (clarity and relevance)

Validity Index	Clarity	Relevance
I-CVI	0.98	0.98
S-CVI	0.98	0.98
S-CVI/UA	0.86	0.86

Phase three

For the two domains, the calculated Cronbach's alpha coefficient for internal consistency was 0.804 which is in the range of accepted reliability. For the knowledge and perception domain, the Cronbach's coefficient was 0.726 while for the practice domain the coefficient was 0.823 suggesting a satisfactory result for reliability (Table 6).

Table 6. Calculated Cronbach's alpha coefficient for internal consistency of each domain

Knowledge and perception domain				
Reliability Statistics				
Cronbach's Alpha			**N of Items**	
0.726			7	
Item-Total Statistics				
	Mean	**Std. Deviation**	**Corrected Item-Total Correlation**	**Cronbach's Alpha if Item Deleted**
Item 1	17.31	2.076	0.226	0.743
Item 2	2.53	0.625	0.539	0.669
Item 3	2.33	0.739	0.389	0.706
Item 4	12.36	3.009	0.556	0.665
Item 5	6.22	1.795	0.58	0.659
Item 6	2.20	0.968	0.519	0.674
Item 7	0.69	0.468	0.28	0.731
Practice domain				
Reliability Statistics				
Cronbach's Alpha			**N of Items**	
0.823			15	
Item-Total Statistics				
	Mean	**SD.**	**Corrected Item-Total Correlation**	**Cronbach's Alpha if Item Deleted**
Item 1	1.8	0.404	0.326	0.82
Item 2	2.422	0.811	0.279	0.823
Item 3	2.622	0.575	0.55	0.806
Item 4	2.511	0.757	0.545	0.806
Item 5	2.533	0.757	0.652	0.799
Item 6	1.711	0.726	0.429	0.814
Item 7	2.244	0.908	0.584	0.803
Item 8	2.155	0.705	0.678	0.797
Item 9	2.422	0.753	0.682	0.797
Item 10	1.622	0.805	0.447	0.813
Item 11	0.755	0.434	0.44	0.813
Item 12	2.33	0.639	0.285	0.823
Item 13	1.77	0.901	0.185	0.829
Item 14	2.977	1.544	0.137	0.832
Item 15	3.4	2.038	0.418	0.814

Pilot study

A total of 45 physicians (56% male and 44% female) were recruited in piloting the final draft of the questionnaire. The age group of the majority (64%) of the participants was between 35-54 years. They were from different professional levels ranging from consultants (11%), specialists (51%), residents (22%), and general practitioners (16%). They were from different specialties (family medicine 29%, internal medicine 24%, general surgery 11%, and other specialties 36%). About half (49%) of the respondents were working in governmental hospitals while 36% were in primary care centers. Only 42% of them were working in private clinics. More than half (56%) of the respondents have more than 10 years of experience in their field of specialty (Table 7).

Table 7. Demographics of the pilot study respondents

Variables		N (%)
Gender	Male	25 (56%)
	Female	20 (44%)
Age group	25- 34 years	7 (15.5%)
	35- 44 years	15 (33.3%)
	45- 54 years	14 (31.2%)
	55 years or more	9 (20%)
Professional level	Consultants	5 (11%)
	Specialists	23 (51%)
	Residents	10 (22%)
	General practitioner	7 (16%)
Specialty	Family medicine	13 (29%)
	Internal medicine	11 (24%)
	General surgery	5 (11.1%)
	Rheumatology	4 (9.5%)
	Cardio-surgery	3 (6.6%)
	Neurology	3 (6.6%)
	Orthopedic	3 (6.6%)
	No specialty	3 (6.6%)
Work setting	Primary care centers	16 (36%)
	Governmental hospitals	22 (49%)
	Tertiary care center	4 (9%)
	Academia	1 (2%)
	Retired	2 (4%)
Working in a private clinic	Yes	19 (42%)
	No	26 (58%)
Years of experience	Less than 5 years	6 (13%)
	5 - 10 years	14 (31%)
	More than 10 years	25 (56%)

Knowledge and Perception domain

In the knowledge and perception domain, the majority of the respondents presented good knowledge of DN in terms of its commonality and effect on patients' quality of life. While only about half of the respondents had good knowledge on the management plan's mainstay and its difficulty along with the effect of DN on mortality rate. In the context of the effect of blood glucose control on DN, the majority of the respondents thought that controlling blood glucose could decrease the incidence of DN while only about one-quarter of the physicians thought that blood glucose control cannot reverse DN (Table 8). Regarding the knowledge of physicians towards vitamins and dietary supplements, about one half of the respondents thought that the dietary supplements are approved by the American Food and Drug Administration (FDA) and that they are quality controlled just like chemical medicines. While about one half of the respondents disagreed with the idea of vitamins and dietary supplements' safety on long-term use, the lack of associated side effects and their lack of tendency to interact with other medications. The respondents were evenly split between supporters and opponents regarding the cost-benefit of vitamins and dietary supplements. About one-half of the respondents believed that vitamin B complex/ B_{12} has no role in the treatment of DN, nor in the prevention of DN. However, near half of the respondents believed that vitamin B complex/ B_{12} supplements are safe for long-term use in the treatment of DN. One-half of the respondents stated that no local (Iraqi) guideline for the management of DN is available and about 34% of them were not sure if such guideline exists. Similarly, about two-thirds of the respondents thought that there was no

definite treatment for DN while about one-third were not sure about the availability of such treatment in the current time. More than one-half of the respondents believed that vascular damage, toxic effects of glucose, and vitamin B_{12} deficiency are the most common causes of DN. Regarding the source of information for the management of DN, respondents rated textbooks and scientific journals, and international guidelines as the most important sources of knowledge (Table 8).

Table 8. Participants' responses in knowledge and perception domain

Knowledge and perception domain				
		Agree	Neutral	Disagree
DN knowledge	DN is a common complication of diabetic patients	32 (71.1%)	13 (28.9%)	0 (0%)
	DN affects patient's quality of life	42 (93.3%)	3 (6.7%)	0 (0%)
	DN increases mortality rate	20 (44.4%)	18 (40%)	7 (15.6%)
	DN is difficult to manage	28 (62.2%)	11 (24.4%)	6 (13.3%)
	DN management plan is based on symptomatic relief	28 (62.2%)	7 (15.6%)	10 (22.2%)
	DN can be reversed by strict blood glucose control	21 (46.7%)	9 (20%)	15 (33.3%)
	DN incidence can be decreased by maintaining strict glucose control	35 (77.8%)	6 (13.3%)	4 (8.9%)
Knowledge of Dietary supplement in DN	Vitamins and dietary supplements are approved by the FDA	22 (48.9%)	13 (28.9%)	10 (22.2%)
	Vitamins and dietary supplements' manufacturing undergoes quality control just like chemical medicines	19 (42.2%)	17 (37.8%)	9 (20%)
	Vitamins and dietary supplements are safe on long term use	12 (26.7%)	15 (33.3%)	18 (40%)
	Vitamins and dietary supplements have no side effects	8 (17.8%)	9 (20%)	28 (62.2%)
	Vitamins and dietary supplements have no interactions with other medications	11 (24.4%)	10 (22.2%)	24 (53.3%)
	The cost of vitamins and dietary supplement worth the efficacy (outcome) provided.	14 (31.1%)	17 (37.8%)	14 (31.1%)
Knowledge of Vitamin B supplements	Vitamin B complex/ B_{12} supplementation can prevent the development of DN	11 (24.4%)	10 (22.2%)	24 (53.3%)
	Vitamin B complex/ B_{12} supplementation can treat DN	12 (26.7%)	15 (33.3%)	18 (40%)
	Vitamin B complex/ B_{12} supplements are safe for long term use in treatment of DN	20 (44.4%)	15 (33.3%)	10 (22.2%)
		Yes	No	Not sure
Do you think that there is a definite treatment for DN?		3 (6.7%)	27 (60%)	15 (33.3%)
Is there any local guideline for the management of DN?		7 (15.6%)	22 (48.9%)	16 (35.6%)

Continued table 8 .

What is the most common cause of DN? (multiple response allowed)		Vitamin B_{12} deficiency	25 (55.6%)	
		Toxic effects of glucose	27 (60%)	
		oxidative stress	15 (33.3%)	
		Vascular damage	31 (68.9%)	
What is (are) the source of information does you follow in managing DN?		Information from senior colleagues	11 (24.4%)	
		Information from colleagues of different specialty	11 (24.4%)	
		Internet and social media	7 (15.6%)	
		Reputable international guidelines, like American diabetes association (ADA), NICE, etc.	18 (40%)	
		Textbooks or scientific journals	26 (57.8%)	
		Own practice	16 (35.6%)	

Practice domain

The majority (80%) of respondents expressed their willingness to prescribe vitamins and/or dietary supplements to their patients with DN in a frequent manner. Vitamin B complex was the most commonly mentioned dietary supplement when they were asked to give an example of dietary supplement that they recommend for their patients. And they recommend these dietary supplements (vitamin B complex) as adjuvant therapy. More than one-half of the respondents considered the effectiveness, safety, cost and patient factors as very important factors in choosing medications for the treatment of DN. More than two-thirds of the respondents chose one of the first line anti-neuropathic agents according to the latest guidelines for DN management, in which, gabapentin was the most chosen agents for the treatment of DN.The respondents' opinions regarding the influence of international guidelines on their practice were in between consulting the guideline and utilizing the guideline. Regarding their management plan of different degrees of DN, more than two-thirds of the respondents recommended the following lines of treatment: lifestyle change, strict control of blood sugar and dietary supplements (including vitamins) for the different severities of the disease. More than half of the respondents recommended an anticonvulsant as an option in managing moderate and severe DN, while about half of the respondents stated their recommendation of combining anti-convulsant, tricyclic antidepressant (TCA), a dietary supplement with or without serotonin-norepinephrine reuptake inhibitor (SNRI) in managing severe DN (Table 9).

Table 9. Participant's responses in practice domain

Practice Domain		
Do you recommend/ prescribe a dietary supplement to your patients with DN	Yes	36 (80%)
	No	9 (20%)
If you answered to the previous question with Yes, how often do you recommend/ prescribe supplements to your patients with DN?	Always	28 (62.3%)
	Sometimes	8 (17.8%)
	Rarely	9 (20%)
Vitamins and dietary supplements in DN are usually prescribed by physicians as:	Treatment	7 (15.6%)
	Adjuvant	26 (57.8%)
	Tonic only	8 (17.8%)
	prophylaxis	3 (6.7%)
	Satisfy the patient (placebo)	1 (2.2%)
The effectiveness of an agent is an important factor in choosing DN medication	Agree	26 (57.8%)
	Neutral	17 (37.8%)
	Disagree	2 (4.4%)
The safety of an agent is an important factor in choosing DN medication	Agree	27 (60%)
	Neutral	11 (24.4%)
	Disagree	7 (15.6%)
Patient preference is an important factor in choosing DN medication	Agree	9 (20%)
	Neutral	16 (35.6%)
	Disagree	20 (44.4%)
Drug - drug interaction is an important factor in choosing DN medication	Agree	19 (42.2%)
	Neutral	18 (40%)
	Disagree	8 (17.8%)
Cost of an agent is an important factor in choosing DN medication	Agree	21 (46.7%)
	Neutral	14 (31.1%)
	Disagree	10 (22.2%)
Patient factors including co-morbidity are important factors in choosing DN medication	Agree	20 (44.4%)
	Neutral	19 (42.2%)
	Disagree	6 (13.4%)
Medical advertisement of an agent is an important factor in choosing DN medication	Agree	10 (22.2%)
	Neutral	11 (24.4%)
	Disagree	24 (53.4%)
A 45 years old male diabetic patient (normal BMI and no comorbidities)	Amitriptyline	5 (11.1%)
	Carbamazepine	2 (4.4%)
	Duloxetine	3 (6.7%)
is complaining of burning and tingling sensation pain in his feet especially at night, what is the drug of choice for this patient?	Gabapentin	18 (40%)
	Pregabalin	7 (15.6%)
	Vitamin B complex	7 (15.6%)
	Vitamin B_{12}	1 (2.2%)
The extent of influences of international guidelines on your practice	I never use them	4 (8.9%)
	I consult them occasionally	22 (48.9%)
	They are fundamental to my practice	19 (42.2%)

Continued table 9.

Management plan of [Mild DN]	Life style change (diet, exercise)	37 (82.2%)
	Strict control on blood sugar	29 (64.4%)
	Supplements (vitamin B complex or Vit B_{12},…etc)	28 (62.2%)
	Anticonvulsants or TCA or SNRI	9 (20%)
	Combination of (anticonvulsant+ TCA and/or SSRI+ supplement)	1 (2.2%)
Management plan of [Moderate DN]	Life style change (diet, exercise)	29 (64.4%)
	Strict control on blood sugar	38 (84.4%)
	Supplements (vitamin B complex or Vit B_{12},…etc)	34 (75.6%)
	Anticonvulsants or TCA or SNRI	22 (48.9%)
	Combination of (anticonvulsant+ TCA and/or SSRI+ supplement)	7 (15.6%)
Management plan of [Severe DN]	Life style change (diet, exercise)	27 (60%)
	Strict control on blood sugar	33 (73.3%)
	Supplements (vitamin B complex or Vit B_{12},…etc)	31 (68.9%)
	Anticonvulsants or TCA or SNRI	25 (55.6%)
	Combination of (anticonvulsant+ TCA and/or SSRI+ supplement)	22 (48.9%)

Discussion

The literature review process revealed no validated questionnaire that is targeted to explore physicians' perception and practice towards the prescription of vitamins and other medicines in DN management. However, the review process found two articles that explored the utilization patterns of anti-neuropathic i.e (TCA, SNRI, anticonvulsants, and opioids) in the UK and Korea [47, 56]. The prescribing preferences of healthcare professionals (physicians, pharmacists, and nurses) regarding anti-neuropathic medications, their knowledge, and beliefs about DN were examined in six researches [48-53]. While Provenzano et al., (2018) have investigated the practice of primary care physicians about the management of chronic pain [54]. Aldossari et al., (2021) had assessed the physicians' knowledge and the tendency of prescribing vitamin B_{12} exclusively for the treatment or prevention of DN in primary care settings [55]. Our study illustrated the ability to produce a questionnaire with good psychometric properties on the physicians' perception and practice toward prescribing vitamin B combination versus antiepileptic drugs in the management of DN along with the factors affecting their choice and the influence of the international guidelines to their current practice. The questionnaire of this study was developed by adapting items from the former-mentioned studies in addition to the self-constructed questions. The content validity was measured in this study since it is an essential step in questionnaire's development. Furthermore, it is an acceptable and important method to reflect the relevance and clarity of the instrument [57]. The content validity indices ranged from 0.8 to 0.9 for both relevance and clarity which is satisfactory and reveals that the questions were relevant and representative of the intended aim of the developed tool [58]. Shi et al., (2012) indicated that I-CVIs $\geq$ 0.78, S-CVI/UA, and S-CVI/Ave $\geq$ 0.8 are considered excellent indices for relevance and clarity. The content validity indices of the constructed questionnaire of this study were within the above-mentioned ranges [59]. The use of Cronbach's alpha in the multiple-item questionnaire was considered as a routine in knowledge, attitude, and practice studies [60], which is used to test and determine the internal consistency (reliability) of a questionnaire in applied research [61]. Nunnally and Bernstein (1978) hypothesized that an alpha value of 0.70 and higher is an acceptable value in the early stages of developing a questionnaire (i.e., exploratory research) [62]. On the other hand, George and Mallery (2003) ranked alpha values according to acceptability into excellent $\geq$ 0.9, good $\geq$ 0.8, acceptable $\geq$ 0.7, questionable $\geq$ 0.6, poor $\geq$ 0.5, and unacceptable $\leq$ 0.5. The Cronbach's alpha coefficient for internal consistency of this study was 0.804 which is considered good [63]. Although the pilot study is time-consuming and leads to considerable data loss, it ensures the feasibility of the developed questionnaire, in other words, it detects any inappropriate and/or complicated questions that would ultimately end up by potential failure of the questionnaire. In our pilot study, the clarity of the questions was confirmed by face-to-

face short interviews with the respondents from different specialties (family medicine, internal medicine, general surgery, endocrinology, rheumatology, and neurology). As expected, the physicians showed a good perception of the commonality of DN, the impact of the disease on quality of life, and the role of glucose control in the etiology of DN and the management plan of the disease. Diverse opinions were noticed regarding the process of manufacturing, FDA approval, safety profile, and the cost-effectiveness of vitamins and dietary supplements. The lack of a local guideline was raised by the respondents as a reason for their different perspectives regarding the use of vitamins and medicines for the management of DN, in which their main source of information were reputable international guidelines like the American diabetes association (ADA) and NICE along with textbooks and scientific journals. However, physicians opted gabapentin, pregabalin, and duloxetine as their first pharmacological choice which was in line with the current international guidelines, the percentage of Iraqi physicians who were adhered to international guidelines was higher than the percentage of the recent Saudi study [(55)]. Although we expected that physicians would prioritize the efficacy and safety in their treatment choice, they also prioritized cost as an important factor in choosing the medication. Interestingly, physicians are willing to prescribe vitamins and supplements for therapeutic purposes as an adjuvant which was consistent with the results of the Saudi study [(55)] in which about half of the physicians rated the efficacy of vitamin B_{12} as moderate in both prevention and treatment of DN. Regarding the management of mild, moderate, and severe DN, although the physicians adhered to the international guidelines that recommended lifestyle changes and strict blood glucose control as a primary intervention for DN. However, they unfollowed these guidelines by recommending vitamins and dietary supplements as an adjuvant treatment. This study has some limitations; first is that despite the fact that Cronbach's alpha is a commonly used test to determine the internal consistency in the literature it has limitations when used as a sole index for internal consistency. Second, the small number of participants in the pilot study was the consequence of the fact that the target population (physicians) are limited in number and hard to reach, and that those who are participated in the pilot study would not be included in the main study (since this article is a part of a larger study and Master degree dissertation); therefore, losing this number would affect the power of the main study. To the best of our knowledge, this study is the first to develop and validate a tool to explore physicians' perceptions and practices regarding the use of vitamins and dietary supplements in the management of DN in different specialties.

Conclusion

This study showed that the constructed questionnaire had good levels of validity (content validity) and reliability that is able to cover different aspects of the current state of perception and practice among physicians regarding the management of DN. The preliminary results of the pilot study showed a good knowledge and perception of the respondents with DN. Even in the absence of a local guideline, the respondents followed the international guidelines in choosing anti-neuropathic agents however, they tended to add vitamin B complex/B_{12} as an adjuvant in their management plan.

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