Role of Neurotropic B Vitamins in the Treatment of Diabetic Neuropathy: Narrative Review

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ABSTRACT

Diabetic neuropathy (DN) is the presence of signs and symptoms that are suggestive of neuropathy in diabetic patients, after excluding other possible causes of nerve damage. Diabetic neuropathy and its complications affect the quality of life, sleep patterns, and daily activities of the patient. Up to date no FDA-approved reversing treatment was found. Studies showed that neurotropic B vitamins (vitamin B_1, B_6 and B_{12}) had an important role in nerve regeneration and included in prescriptions of DN. However, these vitamins were not included in the guidelines of DN management. The aim of this review is to explore the role of neurotropic B vitamins in the treatment of DN including the mechanism of action and the evidence supporting their use. Review of the literature revealed many clinical trials examining the effect of these vitamins (alone or combined) for DN. These vitamins and/or their derivatives had well-illustrated disease-modifying mechanisms on DN. However, larger randomized clinical trials for longer periods are needed to approve their use in DN and to be included in national and international guidelines. This was hindered by the fact that vitamins are non-patentable and therefore fewer funds would be allocated for large randomized clinical trials.

Keywords: Diabetes mellitus, neuropathy, vitamin B, benfotiamine

دور فيتامين –ب- الموجهة للأعصاب في علاج اعتلال العصبي السكري: مراجعه سريريه

الخلاصة: الاعتلال العصبي السكري هو وجود علامات وأعراض توحي بالاعتلال العصبي لدى مرضى السكري، بعد استبعاد الأسباب المحتملة الأخرى لتلف الأعصاب. يؤثر الاعتلال العصبي السكري ومضاعفاته على نوعية الحياة وأنماط النوم والأنشطة اليومية للمريض. حتى الآن لم يتم العثور على علاج عكسي معتمد من إدارة الغذاء والدواء. أظهرت الدراسات أن فيتامينات ب الموجهة للأعصاب (فيتامين ب 1، ب 6، ب 12) كان لها دور مهم في تجديد الأعصاب وأدرجت في وصفات المرضى المصابين بالاعتلال العصبي السكري .ومع ذلك، لم يتم تضمين هذه الفيتامينات في ألاسس العلاجية لمرض الاعتلال العصبي السكري . الهدف من هذه المراجعة هو استكشاف دور فيتامينات ب الموجهة للأعصاب في علاج الاعتلال العصبي السكري بما في ذلك آلية العمل والأدلة التي تدعم استخدامها. كشفت مراجعة البحوث السابقة عن العديد من التجارب السريرية التي تفحص تأثير هذه الفيتامينات (منفردة أو مجتمعة) على الاعتلال العصبي السكري .تحتوي هذه الفيتامينات و / أو مشتقاتها على آليات عمل واضحة التأثير على الاعتلال العصبي السكري .ومع ذلك، هناك حاجة لتجارب سريرية عشوائية أكبر ولفترات أطول للموافقة على استخدامها في الاعتلال العصبي السكري وإدراجها في ألاسس العلاجية الوطنية والدولية. حقيقة أن الفيتامينات غير قابلة للحماية ببراءة اختراع أعاق تخصيص ألاموال اللازمة لاجراء التجارب السريرية العشوائية الكبيرة.

الكلمات المفتاحية: داء السكري، الاعتلال الأعصاب، فيتامين ب، بنفوتيامين

INTRODUCTION

Diabetic neuropathy (DN) is one of the most common and upsetting chronic complication of diabetes mellitus (DM) (1). It is defined as the presence of signs and symptoms that are suggestive of neuropathy in diabetic patients, after excluding other possible causes of nerve damage (2). Diabetic neuropathy is classified into two broad classes according to the site and intensity of nerve damage into symmetric (diffuse) and asymmetric (focal) neuropathy. DN is further subclassified as shown in Table 1. Symmetrical sensorimotor neuropathy is synonymously called DN as it is the most common type of DN affecting about 50% of diabetic patients at some time of the disease course (3, 4).

Table 1 Classification of diabetic neuropathy (5)

Symmetrical	Asymmetrical
- Sensorimotor polyneuropathy - Autonomic neuropathy - Small fiber neuropathy - Treatment-induced diabetic neuropathy - Diabetic cachexia	- Mononeuropathy - Lumbosacral radiculoplexus neuropathy - Cervical radiculoplexus neuropathy - Thoracic radiculopathy - Cranial neuropathy

Pathogenesis of diabetic neuropathy

Up to the time of writing this narrative, researchers had focused on the metabolic and/or redox state (which is defined as the balance between the reactive oxygen species (ROS) and the defensive antioxidants that scavenges the ROS) as a significant aetiologic pathway of DN development. Four metabolic pathways were mainly implicated in the redox state disruption of nerve cells, namely: polyol pathway, the hexosamine pathway, protein kinase C (PKC) isoforms, and increased advanced glycation end products (AGEs) and their subsequent binding to the receptor for advanced glycation products (RAGE). These activated metabolic pathways disrupt the redox state by different mechanisms, either direct increase of ROS production, depleting the important components that is necessary for ROS scavenger or through expression of inflammatory markers with subsequent impaired cell function and death (Fig. 1) (6).

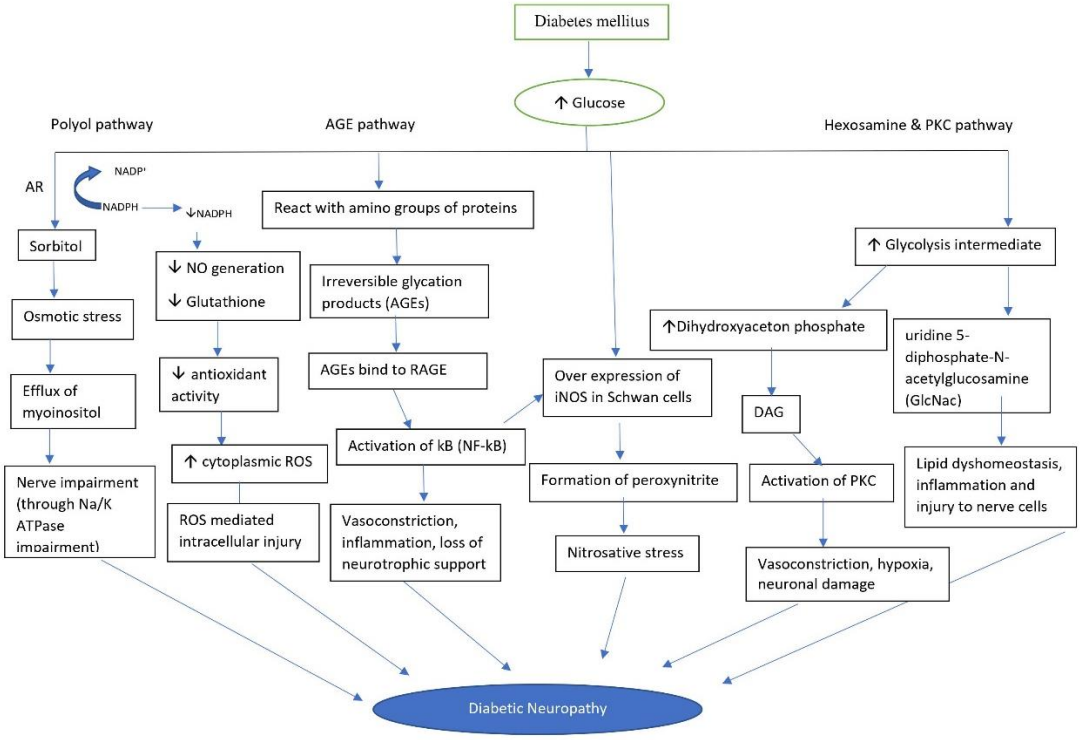

Fig. 1: pathogenesis of DN (AR: aldose reductase, NO: nitric oxide, DAG: diacylglycerol, NF- kB: nuclear factor, RAGE: receptor for advanced glycation products, PKC: protein kinase C, iNOS: endothelial nitric oxide synthase).

Risk factors and complications of diabetic neuropathy

Hyperglycemia, duration of DM, age, and the presence of microvascular complications (like nephropathy and retinopathy) are the most common risk factors for diabetic neuropathy development (7). It was well known that diabetic neuropathy along with peripheral vascular disease composes the main contributing factors of diabetic foot syndrome development. In several cross-sectional studies, diabetic neuropathy was associated with foot ulceration (8, 9), furthermore, its role in foot ulceration was confirmed by a prospective study (10).

Diabetic neuropathy and its complication affect the quality of life, sleep patterns, and daily activities of the patient, they also have a substantial burden on healthcare expenditure. In UK, diabetic foot disease costs more than the collective cost of treating breast, lung, and prostate cancers (11).

Diagnosis

To the time of writing this article, there was no single gold standard tool for the diagnosis of DN (12). The American Diabetes Association (ADA, 2017 update) recommended annual screening by using temperature and/or pinprick sensation for small fibers, a 128 Hz tuning fork for vibration perception by large fibers, and the 10 g monofilament for risk of ulceration (13). Furthermore, nerve conduction studies were commonly used to measure nerve's function and assess the progression of neuropathy and Quantitative sensory testing devices along with questionnaires were used to measure pain and quality of life (14).

Treatment

Due to the complexity of the pathophysiological pathways beyond the development of DN, no FDA (Food and Drug Administration) -approved reversing treatment was found (15). In the current time, international guidelines adopted a management plan that is aimed to prevent the progression of the disease by strict glucose control and appropriate foot care along with pain management (16). Studies showed that vitamin B had an important role in nerve regeneration and included in prescriptions of diabetic patients with DN (17 – 19). A preliminary study conducted at a general hospital in Indonesia (2017), found that 70-85% of geriatric patients with diabetic neuropathy were prescribed B vitamins or mecobalamin (20). Similarly, a Turkish study in 2013 found that about 15% of neuropathic patients' prescriptions contained vitamins (21). However, the latest international guidelines did not include dietary supplements nor vitamins in any line of management (e.g., the National Institute for Health and Care Excellence National (NICE) updated guideline in 2020 (22) and the ADA guideline in 2021(16)). The aim of this review is to explore the role of neurotropic B vitamins (vitamin B_1, B_6 and B_{12}) in the treatment of DN including the mechanism of action and the evidence supporting their use.

Role of neurotropic B vitamins in the treatment of diabetic neuropathy

Vitamin B_1 (Thiamin)

In 1926, Jansen and Donath isolated vitamin B_1 (thiamin) for the first time (23). It is a water-soluble vitamin that is present in a wide range of food from both animal and plant sources. In plants, thiamin is present in its free form while in animal products, the active form's (thiamin diphosphate (TDP)) percentage is more abundant (>95%) (24).

Thiamin diphosphate is an important cofactor for the proper function of three important enzymes in carbohydrate metabolism (which serve as a crucial energy source for nerve fibers) including pyruvate dehydrogenase (which produce acetyl-CoA that is essential for the Krebs cycle), alpha-ketoglutarate dehydrogenase (which promotes the decarboxylation of alpha-ketoglutarate within the Krebs cycle, favoring adenosine triphosphate (ATP) production by glucose oxidation), and transketolase (which regulates the pentose phosphate pathway) (25-27). Furthermore, thiamin abolishes the metabolic dysregulations of (polyol, AGEs, hexosamine, and PKC pathways) caused by high glucose levels (28).

Benfotiamine is a synthetic S-acyl lipid-soluble derivative of thiamin (29). It has a better pharmacokinetic profile in terms of absorption, plasma concentration (about five times greater than that of thiamin), and retention time in the body (30).

Vitamin B_1 and diabetic neuropathy

Jansen et al., (1926) have demonstrated that thiamin deficiency is the cause of a neurological syndrome named Wernicke-Korsakoff or cerebral beriberi (23). In a related finding, in 2007 Thornalley et al., assessed thiamin levels in both diabetic and normal volunteers and demonstrated low plasma levels of thiamin in diabetic patients which was explained by increased renal clearance by 24 and 16 folds in type 1 and type 2 diabetic patients respectively (31).

In the 1940s, several reports had appeared postulating that administering thiamin with adenosine triphosphate (ATP) produces rapid improvement in some neurological disorders (32, 33). From this postulation, the first theory was originated suggesting that thiamin might be used in the treatment of DN and a trial by Shuman and Glipin (1954) was conducted in which they administered ATP

(25mg) with thiamin (20mg) intramuscularly twice daily for 2 to 4 weeks, to 6 patients. Two of six patients developed a subjective improvement with no objective difference, interestingly one patient returned to work for the first time in 18 months after six weeks of the treatment with thiamin and ATP (34).

Winkler et al., (1999) study showed that high dose benfotiamine (320mg/day) containing vitamin B combination is superior to those with moderate dose benfotiamine (120mg/day) containing vitamin B combination and benfotiamine alone (150mg/day) groups in terms of pain reduction, vibration sensation, and current perception threshold. Although this study demonstrated the positive effect of increasing the dose of benfotiamine on the objective measures of neuropathy severity, it still did not prove the effectiveness of benfotiamine alone (35).

In 2005, a double-blind randomized placebo-controlled clinical pilot study conducted by Haupt et al., found that the administration of benfotiamine (400mg/day) for three weeks had a significant positive effect on Katzenwadelet Neuropathy Score, this positive result led to the conduction of a double-blind randomized placebo-controlled phase III clinical study (BENDIP) of 6 weeks (36). The BENDIP trial showed that the administration of benfotiamine 600mg/day improved the Neuropathy Symptom Score (NSS) that was statistically significant in the PP (per protocol) population but failed to be significant in the ITT (intention to treat) population which is the more robust evaluation, however, the period of the trial was too short to the results to be confirmed. In contrast, Fraser et al., (2012) trial concluded that benfotiamine in high dose (300mg/day) had no significant effect on peripheral nerve function, however, the population that was selected for the study were only type I diabetic patients with asymptomatic neuropathy (37).

In 2017, Cvijanović et al., conducted an observational study to evaluate the effect of several agents (including benfotiamine) on the neurophysiological state of patients with symptomatic diabetic neuropathy had confirmed that benfotiamine could improve the neurophysiological parameters of peripheral neurons (38). In 2020, Stirban et al., conducted a clinical trial to confirm and support a previous pilot by Haupt et al., (2005) (39) and a phase III study that was conducted by Stracke et al., (2008) (40) with a longer study period. They administered benfotiamine 600mg/day for three months, followed by 300mg/day until the study ended versus placebo. The outcome measures used was: Michigan Neuropathy Screening Instrument - MNSI questionnaire (MNSIq) and examination (MNSIe), Quality of life (Neuro-QoL™), and neuropathic pain (numerical rating scale - NRS) which were obtained at baseline and 3, 6, and 12 months, however, the trial was stopped prematurely due to technical causes (41).

Interestingly, a recent study on sciatic nerve of hyperglycemic rats was concluded that administration of benfotiamine could attenuate the hyperglycemic effect on the composition of the extracellular matrix of the sciatic nerve more likely by modifying the glucose metabolism (42).

Vitamin B_6

In the 1930s, Rudolf showed that specific cutaneous lesions ‘rat acrodynia’ were developed in young rats who were fed on a semi-synthetic diet (which was free of vitamin B) and supplemented with pure thiamin (B_1) and riboflavin (B_2), the condition was cured by a factor which named vitamin B_6 for the first time (43). Later on, in 1938 Lepkovsky isolated vitamin B_6 for the first time (44).

Vitamin B_6 is an essential water-soluble vitamin that is widely spread in many plant and animal sources (45). Vitamin B_6 is a generic term that refers to six different chemical derivatives of pyridine-based compounds, they are pyridoxine, pyridoxamine, pyridoxal, and their phosphorylated forms in which pyridoxal phosphate (PLP) is the biologically active form (43). PLP is a cofactor for many metabolic and biosynthetic reactions, furthermore, it acts as a direct scavenger for ROS (46).

Pyridoxin (PN) is the most common form of vitamin B_6 that is included in pharmaceutical supplements and other fortified drinks or products (47). All forms of vitamin B_6 including PN undergo conversion to the active form of the vitamin (PLP) by series interactions called the "B_6 salvage pathway" in which pyridoxal kinase (PDXK) converts different vitamers to the phosphorylated form (48). Because vitamin B_6 is highly available in food, its deficiency is somewhat rare and almost related to pharmacological causes such as taking anti-tuberculosis medications or genetic abnormality as seen in PDXK deficiency that ultimately caused peripheral neuropathy (49, 50).

Vitamin B_6 and diabetic neuropathy:

Diabetes mellitus and vitamin B_6 were shown to form a vicious circle. It was shown that the PLP level was decreased in response to acute glucose ingestion in healthy individuals (51). Furthermore, it was shown that the diabetic state opposes an extra demand of vitamin B_6 as the responsible enzymes of amino acid metabolism are highly dependent on B_6 (52). On the other hand, PLP deficiency was shown to disrupt tryptophan metabolism leading to the formation of xanthurenic acid which in turn interferes with the biological activity of insulin causing insulin resistance (53).

The association between diabetic neuropathy and serum level of pyridoxal was first been shown by Davis et al., (1977) (54), who found that serum pyridoxal level was significantly lower in diabetic patients with severe neuropathy in comparison with diabetic patients of similar demography without neuropathy. In 1981, a double-blind controlled study was conducted in which 18 symptomatic diabetic patients were given (50 mg of pyridoxine hydrochloride three times daily) or placebo for four months, the difference between the two groups was insignificant neither in motor nerve conduction velocity nor in symptoms (55). Later on, a similar double-blind controlled trial was conducted and confirmed the former results by Levin et al., (56).

The consumption of supplements containing pyridoxin is common in the population either by over-the-counter pharmaceutical products or prescription medicines. In the past years, concerns were grown about the safety of pyridoxine after publishing several case series and case reports on pyridoxin-induced neuropathy (57 -61). Recently, Hadtstein and Vrolijk (2021), the study proposed that there were several possible mechanisms behind the neurotoxicity of pyridoxin with a conclusion that the most acceptable one is that of PDXK inhibition which ultimately disrupts Gamma-Aminobutyric Acid (GABA) biosynthesis (62). In response to the growing number of case reports the European Food Safety Authority and Netherlands Food and Consumer Product Safety Authority dropped the advised safe upper limit of vitamin B_6 to 25mg/day and 21mg/day respectively (63, 64).

Vitamin B_{12}

The discovery of vitamin B_{12} was first begun by the observation of Minot and Murphy that feeding a pernicious anemic patient with liver cured the disease, this observation led Karl Folkers to discover cobalamin for the first

time in 1948 (65). It is an essential water-soluble vitamin that abundantly occurs with considerable amounts in animal proteins and dairy products (66).

Vitamin B_{12} occurs in four related analogs (differ from each other by the chemical group that binds cobalt) namely: cyanocobalamin, hydroxocobalamin, methylcobalamin, and adenosylcobalamin, the latter two being the active forms (67). The two active forms of vitamin B_{12} act as coenzymes in different reactions in which methylcobalamin is utilized as a cofactor by the enzyme methionine synthase which converts homocysteine to methionine which further promotes methylation of myelin sheath proteins enhancing their stability and simultaneously 5-methyltetrahydrofolate (5-methyl THF) converted into THF that is used in the synthesis of pyrimidine bases with an overall contribution of neuroprotection, maintenance of DNA and red blood cell (RBC) production (68). On the other hand, adenosylcobalamin is involved as a cofactor in enzyme methylmalonyl-CoA mutase, which catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA, preventing its accumulation that will be opposed to being converted to methylmalonic acid (MMA) which was shown to contribute to myelopathy and ultimately causing peripheral and autonomic neuropathy (69) As a consequence, vitamin B_{12} deficiency was linked to peripheral and/or autonomic neuropathy along with other neurological and neurocognitive disorders (70). The recommended daily allowance of vitamin B_{12} for normal functioning is 2.4 micrograms/ day for adult males and non-pregnant females while in pregnant females is 2.6 micrograms/day due to increased demand (71).

Vitamin B_{12} and diabetic neuropathy

According to the latest update of the ADA (2022 update), along with lifestyle modification, metformin was still the first-line therapy in adults with DM type 2 in the absence of contraindication (72). In 1969, Berchtold et al., observed an association between metformin use and vitamin B_{12} deficiency (73). Later on, several trials and case reports (74-76) ascertained the former observation by Berchtold et al., however, there was a lack of evidence of the clinical significance of that association and they all measured B_{12} level solely which is not a reliable biomarker of evident vitamin B_{12} deficiency, instead of measuring MMA level which is recognized to be a more specific biomarker (77). Until recently, Out et al., conducted a long-term trial (4.3 years) to evaluate the effect of metformin on B_{12} and MMA, they concluded its progressive effect on both reducing B_{12} level and increasing MMA with associated worsening of neuropathy symptoms through semi-quantitative neuropathy score assessment (78) although the use of electrophysiological examinations is more sensitive than clinical examination in detecting neuropathy of different severities (79).

In 1986 and 1990, two controlled double-blind trials were conducted in which patients with diabetic neuropathy were enrolled and given either placebo or methylcobalamin in different doses in each trial for about three to four months, they concluded a positive effect on symptoms with no significant improvement in neurophysiological studies (80, 81). Furthermore, Ide et al., (1987) also concluded the same endpoint after conducting a study that included injecting methylcobalamin 2.5 mg intrathecally several times with one-month interval (82).

Recently, a prospective, double-blind, placebo-controlled trial was conducted in which 90 patients with type 2 diabetes with peripheral and autonomic DN were enrolled to receive either 1 mg of methylcobalamin or placebo for one year. They evaluated

different parameters and gained positive results in sural nerve conduction parameters along with MNSIq, level of pain, and questionnaire of quality of life, with no significant improvement in MNSIe and cardiac autonomic reflex tests (CARTS) (83).

Vitamin B complex and diabetic neuropathy

Due to the physiological effects of vitamin B_1, B_6, and B_{12} that had been illustrated in the previous sections, these vitamins are referred to as neurotropic B vitamins (84). They had been implicated in DN through their analgesic/ anti-inflammatory effects and supporting nerve regeneration process. In the context of analgesic and anti-inflammatory effects, it was suggested that some vitamin Bs (especially B_1 and B_{12}) increase the bioavailability of norepinephrine and 5-hydroxytyramin in the inhibitory pathway of pain mediation by interacting with the main mediator (85). On the other hand, it was postulated 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 (86).

Stracke et al., (1996) conducted a double-blind placebo control trial over three months by administering (benfotiamine, B_6, and B_{12}) or placebo to 24 diabetic patients with polyneuropathy, the benfotiamine group had significant improvement in nerve conduction velocity and vibration perception threshold. The results were further confirmed with an extra nine months follow-up of nine patients (87). While Simeonov et al., (1997) conducted an observational study to compare the effect of Milgamma® (benfotiamine, B_6 and B_{12}) in specific and high dose regimes in contrast with Nurobex® (B_1, B_2, B_5, B_6, B_9, and B_{12}) which was administered in less frequent dosing, the study was continued for three months. The Milgamma® group gained a significant improvement in pain sensation and vibration perception which highlights the importance of the neurotropic vitamins in contrast with the other vitamin Bs in addition to the dose-dependent efficacy (88).

On the other hand, Abbas and Swai (1997), conducted a study to evaluate the effect of vitamin B_1 (25mg/day) and B_6 (50mg/day) versus 1 mg of both B_1 and B_6 administered in patients with DN for four weeks, they concluded a significant improvement in terms pain, numbness and paraesthesia in the high dose group (89). Later on, Farvid et al., (2011) (90) conducted a three-armed study in which they enrolled 75 DN patients where they administered either multivitamins and minerals formula that lacks vitamin B, multivitamins and minerals with vitamin Bs (B_1, B_2, B_6, biotin, B_{12}, and folic acid) or placebo for 16 weeks. The group that took multivitamins and minerals with vitamin Bs experienced less neuropathic symptoms while in terms of neurophysiological parameters and MNSI examination there were no significant differences between the three groups.

Fonseca et al., (2013) conducted a double-blind placebo control trial over 24 weeks by administering Metanx® (L-methyl folate, methylcobalamin, and pyridoxal-5-phosphate) or placebo in 214 diabetic patients with neuropathy. The short-term outcome was a significant improvement in terms of symptoms, while neurophysiological parameters showed no significant differences (91).

CONCLUSION:

Although neurotropic B vitamins have shown promising effects by improving the symptoms of DN patients and neurophysiological parameters. Furthermore, these vitamins and/or their derivatives had well-illustrated disease-modifying mechanisms on DN. However, large RCTs

are needed to approve their use in DN and to be included in national and international guidelines. This was hindered by the fact that vitamins are non-patentable and therefore fewer funds would be allocated for large RCTs furthermore, the manufacturers of dietary supplements distinguish a positive phase 2 trial results as satisfactory to encourage their product marketing without going further to phase 3 trial with its highly costly procedure.

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