Contents available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Review

Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy

Qian Xu [a], Jianhong Pan [b], Jingwen Yu [c], Xiaoxia Liu [a], Li Liu [a], Xialin Zuo [a], Ping Wu [a], Houliang Deng [a], Jingjing Zhang [a], Aimin Ji [a,*]

[a] Department of Pharmacy, Zhu-Jiang Hospital, Southern Medical University, Guangzhou, China
[b] Peking University Clinical Research Institute, Beijing, China
[c] Department of Endocrinology, People's Hospital of Hainan Province, Haikou, China

ARTICLE INFO

Article history:
Received 19 November 2012
Received in revised form
12 February 2013
Accepted 25 March 2013
Available online 9 May 2013

Keywords:
Lipoic acid
Methylcobalamin
Combination therapy
Diabetic peripheral neuropathy
Meta-analysis

ABSTRACT

Aims: To compare the efficacy and safety of daily lipoic acid (300–600 mg i.v.) plus methylcobalamin (500–1000 mg i.v. or im.) (LA–MC) with that of methylcobalamin alone (MC) on diabetic peripheral neuropathy (DPN).

Methods: Electronic database were searched for studies published up to November 1, 2012 and study quality was assessed in duplicate. A random or a fixed effect model was used to analyse outcomes which were expressed as risk ratios (RRs) or mean difference (MD). I^2 statistic was used to assess heterogeneity.

Results: Seventeen studies were included. Combined data from all studies showed that the LA–MC combination therapy was significantly superior to MC monotherapy (RR = 1.47; 95% CI: 1.37–1.58). Superiority of the LA–MC combination was shown in nerve conduction velocity (NCV) with WMDs of 6.89 (95% CI: 4.24–9.73) for median motor nerve conduction velocity (MNCV), 5.24 (4.14–6.34) for median sensory nerve conduction velocity (SNCV), 4.34 (3.03–5.64) for peroneal MNCV, and 4.53 (3.2–5.85) for peroneal SNCV. There were no serious adverse events associated with treatment.

Conclusions: The results of the meta-analysis show that treatment with LA–MC for 2–4 weeks is associated with better outcomes in NCV and neuropathic symptoms relative to MC treatment. However larger well-designed studies are required to confirm this conclusion.

Contents

* *Corresponding author at:* Department of Pharmaceutical, Zhujiang Hospital, Southern Medical University, 253 Industry Avenue, Guangzhou 510282, China. Tel.: +86 020 61643500; fax: +86 020 84300639.
E-mail addresses: xiaoqian7666@163.com (Q. Xu), aiminji@163.com (A. Ji).
0168-8227/$ – see front matter
http://dx.doi.org/10.1016/j.diabres.2013.03.033

1. Introduction

Complications of diabetes mellitus (DM) include a variety of neuropathies. DPN is common and has been reported to be present in 12.3% of individuals at diagnosis increasing to up to 50% after 12 year of DM [1–3]. Characterized by chronic paraesthesia, and electrophysiological abnormalities, DPN has a dramatic negative effect on the patient's daily quality of life and function [1,4,5]. The pathogenetic mechanisms of DPN are diverse and not fully understood resulting in limitations to its treatment.

Lipoic acid (LA) was first used therapeutically in Germany to treat diabetic neuropathy and meta-analyses which have evaluated its efficacy and safety provide evidence that LA is a safe antioxidant which could be effective in treating diabetic neuropathy [6,7]. Methylcobalamin (MC) has also been widely used in the treatment of DPN [8,9] and a beneficial effect on nerve conduction has been reported. Recently, in Mainland China, several studies have assessed the efficacy and safety of LA–MC combination therapy compared with MC monotherapy in patients with DPN and have found that the former achieved significantly better results [1,2]. Because of the increasing interest in combination therapy, we conducted a meta-analysis of relevant RCTs which compared combination therapy and MC monotherapy.

2. Methods

2.1. Search strategy

We searched the electronic databases of PubMed, Embase, Cochrane Library and CBM-disc (China Biological Medicine Data-base) without date or language restrictions. The key terms used in this search were (methylcobalamin or mecobalamin) and (lipoic acid or thioctic acid or alpha-lipoic acid) and (diabetic peripheral neuropathy or diabetic neuropathies).

2.2. Inclusion and exclusion criteria

We reviewed each article and retrieved articles based on the following inclusion criteria: (1) RCTs which compared efficacy and safety of LA–MC combination therapy vs. MC monotherapy in patients with DPN. (2) Treatment periods of 2–4 weeks for both groups. (3) Clinical therapeutic efficacy defined by changes in symptoms, tendon reflexes and NCV reported at the end of treatment. We excluded non-randomized trials and studies which administered oral supplements.

2.3. Data extraction

Reviewers screened the full texts from each article independently according to the search strategy. All potentially relevant data which met the inclusion/exclusion criteria were extracted independently by two of the reviewers (XU Q and PAN JH). Extracted data were compared to eliminate errors. Disagreement was solved by discussion and a consensus was finally reached.

2.4. Quality assessment

The methodological quality of included trials was assessed using an established Jadad scale (Table 1). The scores for each article ranged from 0 (lowest quality) to 7 (highest quality). Trials scoring 4–7 points represented good to excellent (high) quality and 0–3 points poor or low quality [10,11].

2.5. Data synthesis

Our meta-analysis was based on outcomes including clinical therapeutic efficacy and NCVs (median MNCV, median SNCV, peroneal MNCV, and peroneal SNCV) which were used in most of the studies as the primary outcomes. Clinical therapeutic efficacy was divided into three categories – markedly effective (disappearance of subjective symptoms, recovered tendon reflex, and NCV increased by at least 5 m/s), effective (alleviated subjective symptoms, improved tendon reflex, and NCV increased by at least 3 m/s) and ineffective (no improvement in symptoms, tendon reflex and NCV). Secondary outcomes, when available, were adverse events.

2.6. Statistical analysis

Dichotomous data are expressed as the risk ratio (RR) and continuous outcomes between groups as weighted mean difference (WMD), both with 95% confidence intervals (95% CI), using a fixed effect (FE) or randomized effect (RE) model for the studies. Z test was used to compare the overall WMD of combination group and the monotherapy group, and differences were considered to be statistically significant when

Table 1 – Methodology quality accessment – modified jadad score (7-point).

Items	Score standard		
	0	2	3
Randomization (A)	Not randomized or inappropriate method of randomization	The study was described randomized	The method of randomization was described and it was appropriate
Concealment of allocation (B)	Not describe the method of allocation concealment	The study was s described as using allocation concealment	The method of allocation concealment was described appropriately
Double blinding (C)	No blind or inappropriate method of blinding	The study was described as double blind	The method of double blinding was described and it was appropriate
Withdrawals and dropouts (D)	Not describe the follow-up	A description of withdrawal and dropout	

two-sided p-value was <0.05 or the 95% CI for RR exceeded 1.0 and WMD exceeded 0.1. Substantial heterogeneity [chi-squared test with degrees of freedom (d.f.)] was represented by I^2 of 50% or more. Significant difference for heterogeneity test was considered when $p < 0.01$. The meta-analysis was performed by RevMan5.0.25 software (Cochrane Collaboration, Oxford, UK) for the above statistical calculations. Publication bias was examined by funnel plots.

3. Results

3.1. Study description

We screened 198 citations and identified 17 studies for further analysis [12–28]. The quality assessment of the included studies is summarized in Table 1. The characteristics of included studies are summarized in Table 2. Most trials were not multicentered and the treatment courses ranged from 2 to 4 weeks. IV administration was commonly used. Many trials reported the number of patients with type 2 diabetes but some did not differentiate the number with type 1 or type 2 diabetes.

3.2. Efficacy

The results of fifteen trials with a total of 1106 patients were entered in our meta-analysis and demonstrated a significant difference in efficacy between LA–MC combination and MC monotherapy. We used the FE model for LA–MC vs. MC group because heterogeneity among the studies measured by the I^2 statistic chi^2 test was insignificant ($p = 0.92$, $I^2 = 0\%$). The combination was superior to monotherapy for efficacy ($p < 0.00001$, RR = 4.03, 95% CI = 1.37–1.58) (Fig. 1). The funnel shape was not absolutely symmetrical (Fig. 2), indicating a potential publication bias.

3.3. Nerve conduction velocities

At entry into the studies, the pooled analysis of NCVs taken as a continuous measurement showed no differences between

Table 2 – Study characteristics.

Source	Number (M + A)/M	Age A + M/M	Sex (men/women)	Treatment drugs sig/day			Study duration/days	Type of diabetes	Diabetes duration (year) A + M/M	Total score
				A + M		M				
				A	M					
Zhaoyy2008 [12]	75 (39/36)	54.5/55.3	38/37	600 ivgtt	500 im	500 im	21	2	9.2/9.2	4
Lihj2008 [15]	78 (39/39)	58.6/57.1	41/37	600 ivgtt	500 ivgtt	500 ivgtt	21	2	9.12/9.21	3
Zhangxl2009 [13]	60 (30/30)	58.8/59.0	34/26	500 ivgtt	500 ivgtt	500 ivgtt	21	2	NR	3
Suoln2009 [14]	64 (32/32)	65.0/65.0	38/36	600 ivgtt	500 ivgtt	500 iv	14	2	8.91/8.97	3
Zhangch2009 [16]	60 (32/28)	57.8/54.4	31/29	600 ivgtt	500 im	500 iv	21	NR	9.2/9.0	3
Xinyy2009 [17]	60 (30/30)	52.3/52.3	30/30	600 ivgtt	500 iv	500 iv	14	2	8.7/8.7	3
Jiazhm2010 [18]	80 (56/24)	48.0/48.0	46/34	600 ivgtt	500 im	500 iv	15	2	9.54/9.54	4
Zhaoyh2011 [19]	80 (40/40)	65.4/66.2	47/33	300 ivgtt	500 im	500 im	21	NR	8.3/8.3	3
Wangzhh2011 [20]	60 (32/28)	56/55.5	31/29	600 ivgtt	500 ivgtt	500 ivgtt	21	NR	9.8/9.7	3
Zhuyp2011 [21]	84 (42/42)	56.0/56.0	37/45	450 ivgtt	500 iv	500 iv	14	NR	9.8/10.0	3
Luosj2011 [22]	72 (38/34)	57.5/56.7	38/34	600 ivgtt	500 im	500 im	14	2	7.9/8.3	3
Songxc2011 [23]	84 (42/42)	57.0/62.0	39/45	600 ivgtt	500 ivgtt	500 ivgtt	14	2	NR	3
Gaoar2011 [24]	138 (46/46/46)	62.0/61.0	48/44	600 iv	500 iv	500 iv	14	NR	8.6/8.6	3
Linyl2012 [25]	102 (52/50)	50.6/51.8	39/63	600 ivgtt	500 iv	500 iv	14	NR	7.9/7.5	3
Yangy2012 [26]	86 (43/43)	55.7/55.7	52/34	600 iv	500 iv	500 iv	14	2	2.4/2.4	3
Cuify2012 [27]	65 (35/30)	41.2/41.6	38/27	450 ivgtt	500 iv	500 iv	28	2	NR	3
Zhangrq2012 [28]	60 (30/30)	65.8/65.9	36/24	600 ivgtt	1000 iv	1000 iv	21	2	8.5/8.5	3

Notes: A, lipoic acid; M, methylcobalamin; iv, intravenous; ivgtt, intravenous infusion; im, intramuscular; NR, not reported.

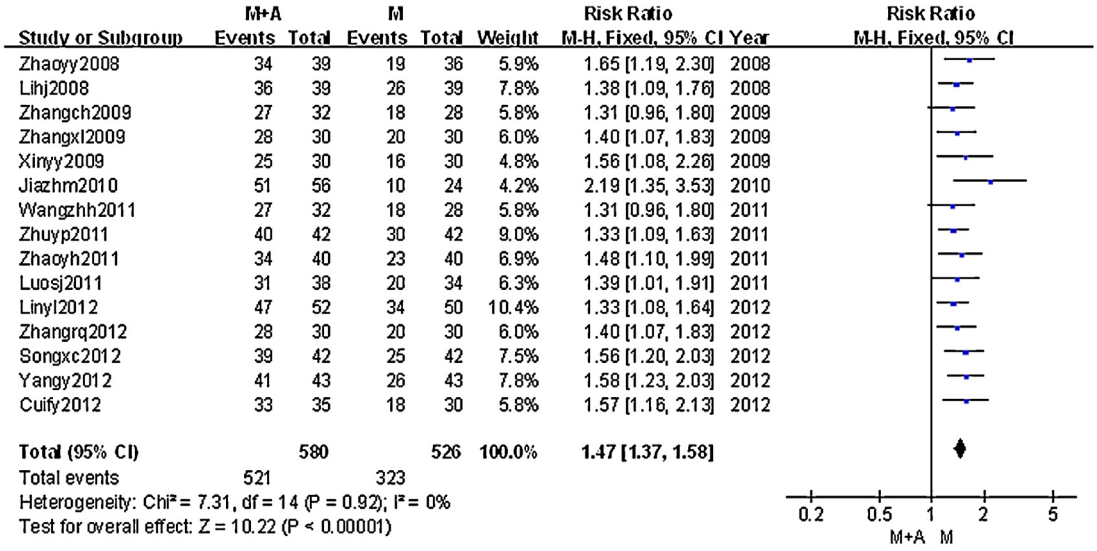

Fig. 1 – Comparison of efficacy of LA–MC group and MC alone group for DPN. *Notes*: A, lipoic acid; M, methylcobalamin.

the groups for any of the studies. After 2–4 weeks, the changes in NCVs differed significantly between the LA–MC combination and MC monotherapy groups (Fig. 3). Thirteen RCTs involving 1038 subjects reported median MNCV as an outcome. Significant between-studies heterogeneity was observed ($p < 0.00001$; $I^2 = 97\%$). The estimated WMD for LA–MC and MC monotherapy was 6.89 (95% CI: 4.24–9.73). For median SNCV, significant heterogeneity between studies was observed ($p < 0.00001$; $I^2 = 77\%$). There were 13 trials evaluating 978 patients showing a statistically significant effect in favour of LA–MC combination v MC monotherapy ($p < 0.00001$; MD = 5.24, 95% CI = 4.14–6.34). Fourteen trials with a total of 1058 patients reported peroneal MNCV as an outcome. Heterogeneity between trials was significant ($p < 0.00001$, $I^2 = 88\%$). Peroneal MNCV was statistically improved in the combination v monotherapy group ($p < 0.00001$, MD = 4.34, 95% CI = 3.03–5.64). For peroneal SNCV (12 trials $n = 918$), the result of heterogeneity between studies for the two groups was significant ($p < 0.00001$, $I^2 = 91\%$). The combination group was statistically superior to the MC group ($p < 0.0001$, OR = 4.53, 95% CI = 3.20–5.85).

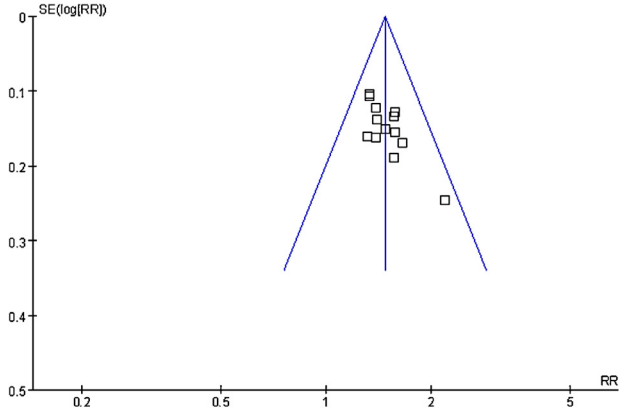

Fig. 2 – Funnel plot for LA–MC group vs. MC alone group for DPN.

3.4. *Adverse events*

Administration of LA at doses of 300–600 mg/day and MC at doses of 500–1000 μg/day intravenously for 2–4 weeks was well tolerated and no serious treatment-related adverse events were observed in the combination group. Only a few mild adverse effects such as mild swelling and pain at the injection site (5 cases) [17,28], headache (1 case) [23], nausea (1 case) [23] were reported in the combination group, and nausea (1 case) [23] in MC group. Because studies did not report these events in detail, we were unable to precisely compare rates of adverse events.

4. Discussion

Diabetes poses a growing burden in the world [29]. In the first decade of this century, the prevalence of DM among men and women in China has increased from 2.6% to 9.7% giving an estimated total of 92.4 million people with DM [30]. The Rochester Diabetic Neuropathy Study suggested that up to 65% of individuals with type 1 or type 2 diabetes have peripheral neuropathy [31]. The pathophysiology of diabetic neuropathy includes increased formation of advanced glycated end products, alterations in protein kinase C pathways [32], increased polyol pathway activity, decreased nitric oxide/impaired endothelial function [33], reduced (Na^+/K^+)-ATPase activity [34], and homocysteinemia [35].

The mechanisms of action of LA for the treatment of DPN may be related to improvements in nerve blood flow by means of anti-oxidation [36–38] and endothelial dysfunction by reducing levels of interleukin 6 and plasminogen activator 1 in plasma [39]. LA has also been reported to increase glucose uptake by nerve cells [40], (Na^+/K^+)-ATPase activity [41], and improve nitric oxide-mediated endothelium-dependent vasodilation [42]. Neuropathic symptoms, but not motor or sensory NCV, were improved by LA alone [6]. Han et al. reported that treatment with LA can improve NCVs, however, patients also

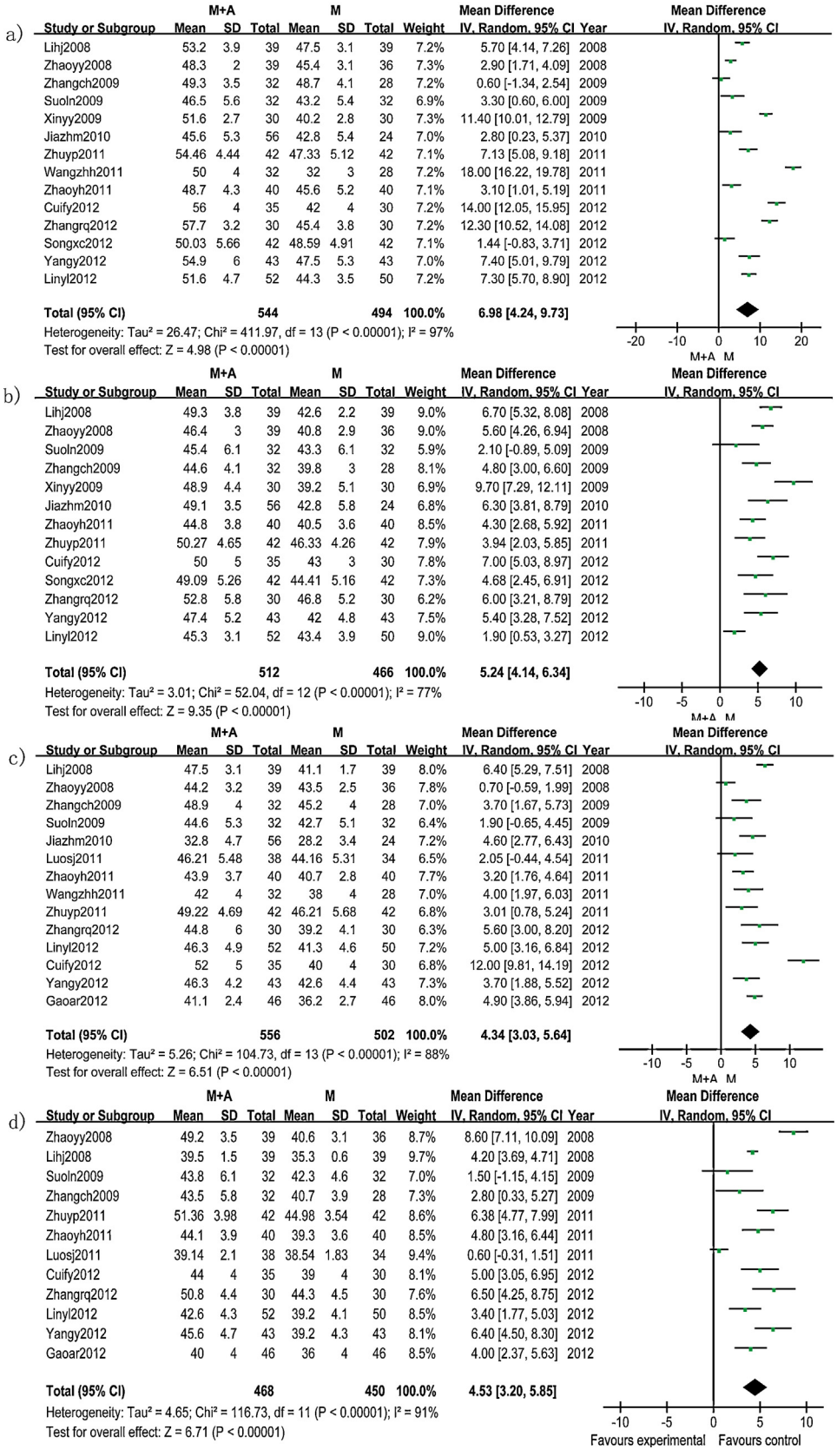

Fig. 3 – Comparison of NCVs, including (a) median MNCV; (b) median SNCV; (c) peroneal MNCV; and (d) peroneal SNCV, improvement of LA–MC group with MC alone group for DPN. *Notes*: A, lipoic acid; M, methylcobalamin.

received treatment with other drugs including MC or prostaglandin [7]. In short, studies suggest that using LA alone may not be sufficient to improve NCVs.

Studies with MC have reported beneficial effects and safety on recovery of peripheral nerve structure and function [8,43–45]. MC can directly accelerate transmethylation in nerve tissues, promote conversion of homocysteine to methionine, increase myelination, neuronal differentiation and replication, and increase biologic synthesis of phospholipids and nucleic acids. Mizukami et al. suggested that correction of impaired neural signal of protein kinase C and oxidative stress-induced damage may play a major role in the beneficial effects of MC on DPN [46].

There are several limitations of our meta-analysis that should be taken into account when interpreting the results. First, most of the studies included in this review had poor methodological quality. They were of small sample size and did not describe withdrawals or dropouts. Even if the study referred to the withdrawal or dropout, it did not explain whether they performed an intention-to-treat analysis. Second, no studies have yet assessed long-term effectiveness in terms of efficacy, harms and health outcomes.

In conclusion, although some limitations exist in this meta-analysis, treatment with LA (300–600 mg i.v.) plus MC (500–1000 mg i.v. or im.) once a day for 2–4 weeks resulted in better improvement in neuropathic symptoms and NCVs compared with administration of MC alone. Moreover, compared with MC alone, LA–MC combination therapy was not associated with more severe adverse events in patients with DPN. However due to poor methodological quality of the studies included in this meta-analysis, well-designed multicenter RCTs are required to confirm these findings.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors have no relevant financial involvement with any organization with a financial interest in with the materials discussed in the manuscript. All authors conceived the study and developed the protocol.

REFERENCES

[1] Solomon T, Dinesh S. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 2012;28(1):8–14.
[2] Spruce MC, Potter J, Coppini DV. The pathogenesis and management of painful diabetic neuropathy: a review. Diabet Med 2003;20:88–98.
[3] UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[4] Ziegler D. Treatment of diabetic polyneuropathy update 2006. Ann N Y Acad Sci 2006;1084:250–66.
[5] Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabet Care 2010;33(10):2285–93.
[6] Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant a-lipoic acid: a meta-analysis. Diabet Med 2004;21:114–21.
[7] Han TT, Bai JF, Liu W, Hu YM. A systematic review and meta-analysis of a-lipoic acid in the treatment of diabetic peripheral neuropathy. Eur J Endocrinol 2012;167:465–71.
[8] Zhang YF, Ning G. Mecobalamin. Expert Opin Investig Drugs 2008;17(6):953–64.
[9] Kathleen A, Head ND. Peripheral neuropathy: pathogenic mechanisms and alternative therapies. Altern Med Rev 2006;11(4):294–329.
[10] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1–12.
[11] David M, Pham B, Alison J, Deborah JC, Alejandro RJ, Michael M, et al. Does quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;22(8). 352(9128):609–13.
[12] Zhao YY, Li H, Fang ZY, Ma J, Hu B. Combined therapeutic effects of α-lipoic acid and mecobalamin on diabetic peripheral neuropathy. J Pract Med 2008;24(24):4289–90.
[13] Zhang XL, Feng YL, Zhou BA, Wei GY. Effects of mecobalamin and α-lipoic acid on diabetic peripheral neuropathy. Shandong Med J 2009;49(7):48–9.
[14] Suo LN, Zhang D. Effects of lipoic acid and mecobalamin on diabetic peripheral neuropathy. J Tradit Chin Med 2009;24(6):1104–5.
[15] Li HJ. Effects of α-lipoic acid and mecobalamin on diabetic peripheral neuropathy. Chin J Misdiag 2008;8(36):8847–8.
[16] Zhang C, Yu XJ, Shi WW. Combined therapeutic effects of α-lipoic acid and mecobalamin on diabetic peripheral neuropathy. Heilongjiang Med Pharm 2009;32(6):78–9.
[17] Xin YY. Effects of α-lipoic acid on diabetic peripheral neuropathy. China Modern Doctor 2009;49(34):45–9.
[18] Jia ZM. Combined therapeutic effects of α-lipoic acid and mecobalamin on diabetic peripheral neuropathy. Chin J Mod Drug Appl 2010;13(4):143–4.
[19] Zhao YH, Li H, Fang ZY, Ma J, Hu P. Effects of lipoic acid combined with mecobalamin on diabetic peripheral neuropathy. China Modern Doctor 2011;49(35):56–7.
[20] Wang ZH, Yang XJ, Fan F. Effects of lipoic acid combined with mecobalamin on diabetic peripheral neuropathy. J Pract Med 2011;18(8):863–4.
[21] Zhu YP, Zhang H. Effects of lipoic acid combined with mecobalamin on DPN. Med Inform 2011;24(8):24–5.
[22] Luo SJ. Effects of lipoic acid combined with mecobalamin on diabetic peripheral neuropathy. Modern J Integr Tradit Chin Western Med 2011;20(3):303–4.
[23] Song XC, Ling GM, Xie QP. Therapeutic effect of lipoic acid on diabetic peripheral neuropathy based on 84 cases clinical observation. Intern Med 2011;6(5):413–5.
[24] Gao AR, Zhang XH. Clinical value study of α-lipoic acid combined with Mecobalamin in treating Diabetic Peripheral Neuropathy. Chin Remed Clin 2011;11(12):1452–3.
[25] Lin YL, Zhong RF. Effects of Mecobalamin and α-lipoic acid on diabetic peripheral neuropathy. China Modern Doctor 2012;19(12):53–4.
[26] Yang Y, Song XH, Liu JY, Qu B. Clinical value study of α-lipoic acid combined with Mecobalamin in treating Diabetic Peripheral Neuropathy. China Medical Herald 2012;9(8):86–7.
[27] Cui FY, Shi ZD. Clinical value study of α-lipoic acid combined with Mecobalamin in treating Diabetic Peripheral Neuropathy. Chin J Pract Med 2012;39(9):107–8.

[28] Zhang RQ. Clinical value study of lipoic acid in treating Diabetic Peripheral Neuropathy. Clin Med China 2012;28(6):614–6.
[29] Whiting DR, Guariguata L, Weil C, Shaw J. IDF Diabetes Atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabet Res Clin Pract 2011;94:311–21.
[30] Li NJ. From Kingdom to Kingdom, but hopefully not again. Diabet Res Clin Pract 2012;10:1–2.
[31] Dyck PJ, KarnesJL, O'Brian PC. The Rochester Diabetic Neuropathy Study: reassessment of tests and criteria for diagnosis and staged severity. Neurology 1992;42:1164–70.
[32] Eichberg J. Protein kinase C changes in diabetes: is the concept relevant to neuropathy? Int Rev Neurobiol 2002;50:61–82.
[33] Cameron NE, Cotter MA. Metabolic and vascular factors in the pathogenesis of diabetic neuropathy. Diabetes 1997;46:S31–7.
[34] Stevens MJ, Dananberg J, Feldman EL, Lattimer SA, Kamijo M, Thomas TP, et al. The linked roles of nitric oxide, aldose reductase, and, (Na^+, K^+)-ATPase in the slowing of nerve conduction in the streptozotocin diabetic rat. J Clin Invest 1994;94:853–9.
[35] Ambrosch A, Dierkes J, Lobmann R. Relation between homocysteinaemia and diabetic neuropathy in patients with type 2 diabetes mellitus. Diabet Med 2001;18:185–92.
[36] Nagamatsu M, Nickander KK, Schmelzer JD, Raya A, Wittrock DA, Tritschler H. Lipoic acid improves nerve blood flow,reduces oxidative stress, and improves distal nerve conduction in experimental diabetic neuropathy. Diabet Care 1995;18:1160–7.
[37] Coppey LJ, Gellett JS, Davidson EP, Dunlap JA, Lund DD, Yorek MA. Effect of antioxidant treatment of streptozotocin-induced diabetic rats on endoneurial blood flow, motor nerve conduction velocity, and vascular reactivity of epineurial arterioles of the sciatic nerve. Diabetes 2001;50:1927–37.
[38] Kunt T, Forst T, Wilhelm A, Tritschler H, Pfuetzner A, Beyer J. a-Lipoic acid reduces expression of vascular cell adhadhesion of human monocytes after stimulation with advanced glycation end products. Clin Sci 1999;96:75–82.
[39] Sola S, Mir MQ, Cheema FA, Khan-Merchant N, Menon RG, Khan BV. Irbesartan and lipoic acid improve endothelial function and reduce markers of inflammation in the metabolic syndrome: results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) study. Circulation 2005;111:343–8.
[40] Kishi Y, Schmelzer JD, Yao JK. Alpha-lipoic acid: effect on glucose uptake, sorbitol pathway, and energy metabolism in experimental diabetic neuropathy. Diabetes 1999;48:2045–51.
[41] Stevens MJ, Obrosova I, Cao X. Effects of DL-alpha-lipoic acid on peripheral nerve conduction, blood flow, energy metabolism, and oxidative stress in experimental diabetic neuropathy. Diabetes 2000;49:1006–15.
[42] Heitzer T, Finckh B, Albers S, Krohn K, Kohlschutter A, Meinertz T. Beneficial effects of a-lipoic acid and ascorbic acid on endothelium-dependent, nitric oxide-mediated vasodilation in diabetic patients: relation to parameters of oxidative stress. Free Radic Biol Med 2001;31:53–61.
[43] Li NJ. From Kingdom to Kingdom, but hopefully not again. Diabetes Res Clin Pract 2012;1–2.
[44] Kuwabara S, Nakazawa R, Azuma N, Suzuki M, Miyajima K, Fuku T. Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. Intern Med 1999;38:472–5.
[45] Sun Y, Lai S, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials. Acta Neurol Taiwan 2005;14:48–54.
[46] Mizukami H, Ogasawara S, Yamagishi S, Takahashi K, Yagihashi S. Methylcobalamin effects on diabetic neuropathy and nerve protein kinase C in rats. Eur J Clin Invest 2011;41(4):442–50.