Vitamin Bs and other agents in diabetic neuropathy: a work in progress

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Overview

- Metanalysis / review of Vitamin Bs in DPN
- Vitamin B1, B6 & B12 in Diabetic polyneuropathy (DPN)
- Vitamin B12
- Vit B12 & Metformin
- Alpha-Lipoic Acid(ALA) in DPN
- Gamma-linolenic acid (GLA) in DPN
- Vitamin D & E in DPN
- Key Messages
What do we need to do?

- Glycemic control → foremost target
- Vascular risk factors → multifactorial intervention (STENO2)
- High residual risk of DPN
- Conventional agents in painful DPN → poor response & side-effects
- Vit B1, B6 & B12 → major vitamin B complex → act as coenzymes & cofactors
Vit B combo→↓pain, no clarity on efficacy of individual B vits nor mechanisms

Combo of vit B1, B6 & B12 for 7–9 days dose-dependently improved tactile allodynia, formalin hyperalgesia, sensory NCV in diabetic rats.

All 3 individual B vits participated with variable efficacy.

Only vit B6 improved sensory NCV slowing when given alone.

Markers of oxidative stress (lipid & protein oxidation) & inflammation(COX-2 & TNFα) in nerve were not significantly affected
- Vit B provides inconsistent short-term improvement & not better than placebo in terms of pain relief
- Limited data in RCTs of vit B for treating peripheral neuropathy & evidence is insufficient to determine whether vit B is beneficial or harmful.
- Lack of evidence of vit B may be due to genuine lack of therapeutic effect.
- Adequate dose for treatment → unknown
- In 2 large trials comparing different doses of vit B complex, some evidence that higher doses resulted in significant short-term reduction in symptoms
- Vit B for 2-8 wks was less efficacious in clinical & NCS outcomes vs ALA, cilostazol
Vitamin Bs in DPN: Study Problems

- Most RCTs not double-blind → selection bias; small number → ↓ validity
- Methodological uncertainties, differences in populations,
- Animal studies, in vitro vs in vivo studies → contradictory
- Variability of intervention (multicomponent vit B, injected vs oral) & diverse scoring systems used in measuring outcomes
- No assessment of baseline deficiency → effect after correction
- High quality RCTs needed → type of vit B compound, route, duration, effects of combining vit Bs & sensitive assessment tools
- Future subgroup analysis of diabetic participants with or without deficiency.
Case Study

- 64yr man, on veg diet, T2DM for 3 yrs on Metformin 2gm/d, statin 10mg
- C/O tingling, numbness & parasthesia in legs + ↓ vision
- BP-144/92, objective ↓ pain, touch, JPS, & VPT distally in legs + normal knee & ankle DTR, motor-N, mild optic atrophy, no DR
- Hb-12.2, MCV-96, normocytic, HbA1C-7.8%, LDLC-110mg/dl, Tg-320/mg/dl, HDL-34mg/dl, Cr-0.9mg/dl, Urine ACR-18
- Cbl-233pmol/L (N>221), tHcy-32 mmol/L (n<15), ↑ MMA, ↓ folate
- Issues- peripheral neuropathy- multifactorial → elderly, vegan, short DM duration, high dose metformin, OA, lowish Cbl, ↑ Tg, Hcy
- Cbl deficiency → neuropathy → irreversible & precedes megaloblastic anaemia
Effectiveness of Vitamin B12 on Diabetic Neuropathy: Systematic Review of Clinical Controlled Trials

- VitB12 combo & pure MC → ↓ symptoms, inconsistent effect on VPT, NCV

- Only one RCT excluded subjects with vit B12 deficiency

- More high quality double-blind RCTs with subgroup analysis of diabetics with or without B12 deficiency in clinical trials of vitamin therapy is important.
Vitamin B12 in T2DM patients treated with metformin

- Ca in ileum $\rightarrow$ ↑vitB12-IF uptake by ileal cell receptor, metformin $\rightarrow$ ↓ Ca availability at ileal

- NHANES (1999-2006): 5.8% of T2DM > 50 yrs on metformin for 5 years vit B12 deficiency vs 2.4% not on metformin & 3.3% of nondiabetics

- NHANES $\rightarrow$ oral Cbl in chronic metformin unsuccessful in correcting Cbl levels *Diabetes Care* 2012

- 24-wk 1.5mg/d of oral MC in DPN $\rightarrow$ ↓Symptoms, no new symptoms but not NCV *Journal of Diabetes Mellitus* (2012) 408-412

- Each 1 g/day increment in metformin dose $\rightarrow$ OR of 2.88 risk of Cbl deficiency.
Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: Multicentre RCT
BMJ 2010;340:c2181

- 390 T2DM on insulin & 850mg metformin or placebo TID for 4.3 years.
- Vit B12 <150 pmol/L: 9.9% vs 2.7%
- Vit B-12: ↓19% (P<0.001) & progressive over time requiring substitution
- ↑Absolute risk of deficiency by 7% point
- ↓Folate −5% (P=0.033) & ↑homocysteine
Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency

- Optimal screening → at initiation of metformin → 1–2 yrly
- Elderly diabetics on long-term high dose metformin, presenting as PN without haematological manifestations is misdiagnosed as DPN
- Parenteral route preferable if neurodeficits → ↑risk of irreversibility.
- Initial parenteral Cbl → 1 mg/day for 1 wk → 1 mg/wk for 4 weeks
- Duration of Cbl supplementation → triggering factor
- High dose oral Cbl as a definitive treatment not yet been fully validated
- Unknown if Ca reverses Cb deficiency → Ca not prescribed for prevention/treatment
- DPN resemble ↓VitB12 neuropathy → annual 1 mg Cbl inj on long-term metformin?
Pyridoxine (Vitamin B6) in Diabetic DPN

- Active vit B6 → Pyridoxal 5’-phosphate → ↓ glycosylation of proteins


- Pyridoxine (25mg) for 6 wks → ↓ subjective symptoms in 10 DPN pts.

- No objective assessments nor vit B6 status measured. *JAmPodiatry Assoc. 68;*, 1978

- 3 subsequent double-blind placebo-RCTs found no benefit in DPN. *J Am Podiatry Assoc* 1984; *Diabetes Care* 1981; *Diabetes Care* 1983;

- Double-blind study → vit B6 deficiency was not a factor in DPN & treatment was not effective in 18 symptomatic DPN pts. *DIABETES CARE* 4-606-609, 1981

- Only one pt had low PP at start of study.

- RDI → 1.4-2.0mg/d, dosage → ? Overdose → peripheral sensory neuropathy *(Schaumburg 1983)*
Benfotiamine (Vit B1) in DPN

- Benfotiamine → fat-soluble vitB1, 5 times ↑ peak plasma \( (Stracke\ 1996) \)
- Benfotiamine → ↑ transketolase → ↓ AGE.
- One trial with oral benfotiamine for 8 wks → small benefit in VPT
- BEDIP 3; 2005: PO 50mg 4 times/d → ↑ Neuropathic Symptoms
- BENDIP: 181 DPN: 6 wks 300/600 mg/d benfotiamine → ↑ symptom scored \( Exp\ Clin\ EndocrinolDiabetes,\ 2008 \)
- ↑ Improvement at higher benfotiamine dose & ↑ therapy duration
- RDI 1.0-1.5 mg/d; High oral doses (40mg/d) → deficiency states?
Alpha-Lipoic Acid (ALA)

- ALA: endogenous antioxidant,↑ endoneurial nerve blood flow, glucose uptake.
- Meta-analysis of iv ALA→↓symptoms, neurodeficits, safe with NNT of 6.3  
  *Diabet Med. 2004*
- Oral/iv ALA in DPN→ review of 15 trials→ ↓neuropathic symptoms & deficits.
- SYDNEY 2→ oral ALA 600mg/d for 5wks in symptomatic DPN → optimum risk-benefit in improving symptoms & deficits  
  *Diabetes Care 3: 108, 2006*
- NATHAN1→oral ALA 600-1200mg/d:4yrs in 460 pts→↓progression in mild/mod DPN.  
  *Diabetes Care. 2011*
- Appropriate pt selection, optimal treatment duration, cost-benefit analysis?  
  *Angiology 2012*

Effect on neuropathic symptoms and signs than low doses. These findings require confirmation. Small trials suggested that treatment with vitamin B for two to eight weeks was less efficacious than alpha-lipoic acid, cilostazol or cytidine triphosphate in short-term improvement of clinical and NCS outcomes. These also require confirmation.
Gamma-linolenic acid (GLA)

- GLA → component of myelin → Δ-6-desaturase (↓ in DM) → prostaglandin E₁ → anti-inflammatory, antiplatelet, vasodilatation

- RCT in 22 type 1 & 2 mild DPN → 360 mg/d of GLA (6 mths) → ↑ overall symptom scores  
  *Diabet Med 1990*

- RCT of 51 type 1 & 2 DPN → 480 mg/d GLA for 1 yr → no improvement in VPT  
  *Diabetologia 1997*

- 45 T2DM with DPN → 360mg/d GLA or 360mg/day GLA+1g/d ALC for 6mths → improvement in NCV & latencies in both, more with combo  
  *Turkish J of Endo. & Met. 2000*
Vitamin D & E in DPN

- Vit D deficiency → independent risk factor for DPN & RCTs required to confirm

- Vit D deficiency more common in diabetics with symptomatic DPN

- Vit D deficiency → ↓ pain threshold & NGF which improves with correction

- Lee et al. found significant reduction in pain score with oral vit D3 in 51 DPN pt

- Vit E (900 IU) for 6mth on nerve function was evaluated in RCT of 21 mild/mod DPN → ↑ median & tibial motor NCV improved *Diabetes Care 1998.*
Key Messages

- Vit B1, B6 & B12 in treatment of DPN not established & not recommended as a standard or routine therapy without underlying deficiencies. Diabetes Care 31:2008
- No significant benefit in DPN: AAN 2013
- No clear evidence of benefit from vitamin supplementation in diabetes vs general population, without underlying deficiencies. Diabetes Care; 2004
- Vitamin needs in diabetics adequately by RDAs from natural food
- Elderly, pregnancy, low calorie diets, vegans, CHF, MI →↑ deficiencies
- Assess B12 in DPN on long term metformin, vegans, elderly,
- Labs measuring micronutrients→unsatisfactory. Plasma ≠ functional
- ALA approved in Germany for DPN, but lack long-term safety & effectiveness data