What to consider in the use of Vitamin B12 in the treatment of Peripheral Neuropathy?

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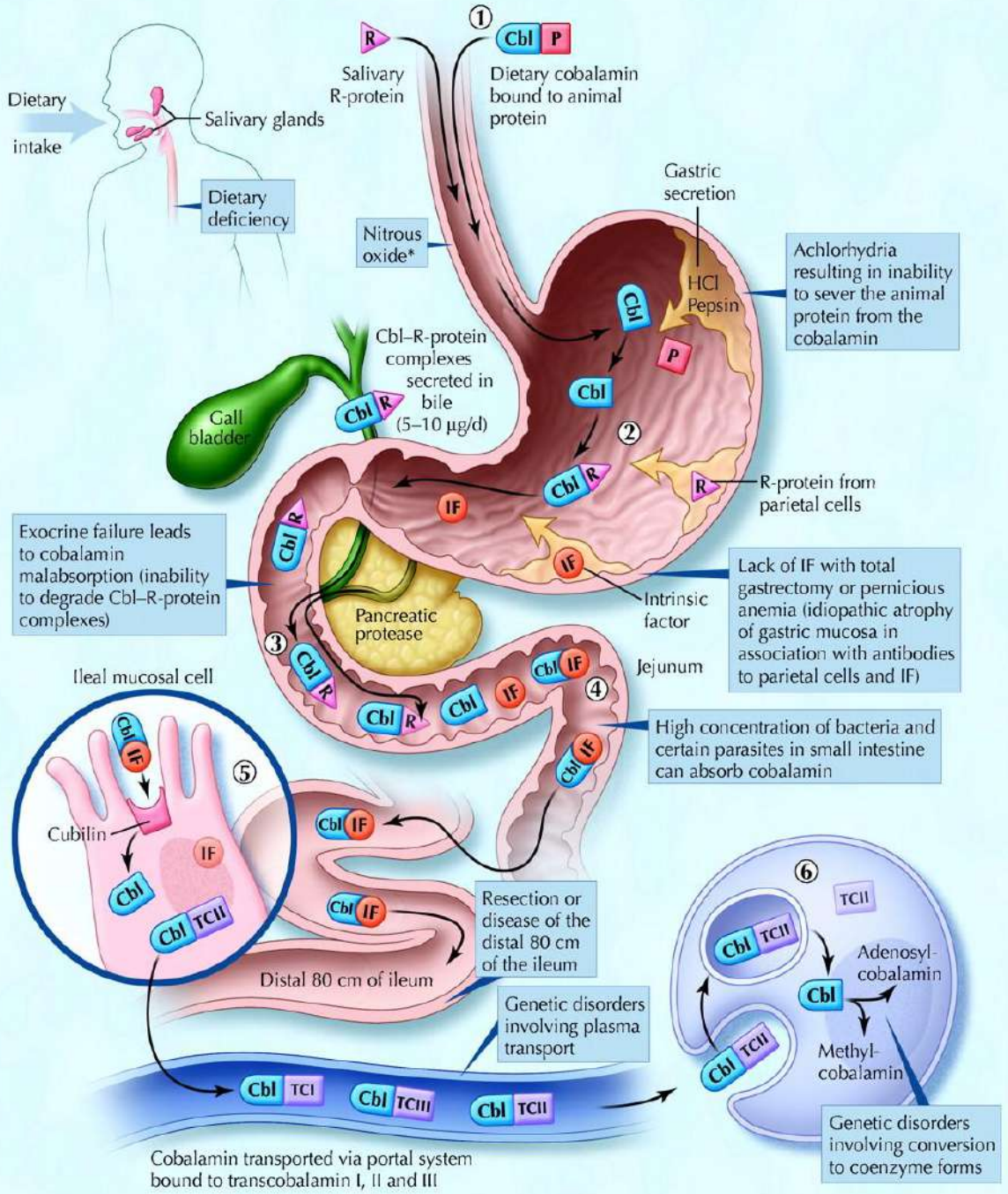
Vitamin B12: Overview

- Vitamin B12, also known as cobalamin, is an important water-soluble vitamin involved in red blood cell production, brain health, and DNA synthesis
- Current intake recommendations are 2.4 µg/day for adults, slightly more during pregnancy (2.6 µg/day) and lactation (2.8 µg/day)
- Cobalamin is stored in the liver, 3 – 5 mg being present in normal subjects.
- The average people stores 2,000-3,000 µg B12. About 60% of the total amount of B12 in the body is stored in the liver and 30% is stored in the muscles.64
- Different analogs of Cobalamin : Methylcobalamin (MeCbl) , cyanocobalamin (CyCbl), adenosylcobalamin (AdoCbl), hydroxocobalamin (HyCbl)

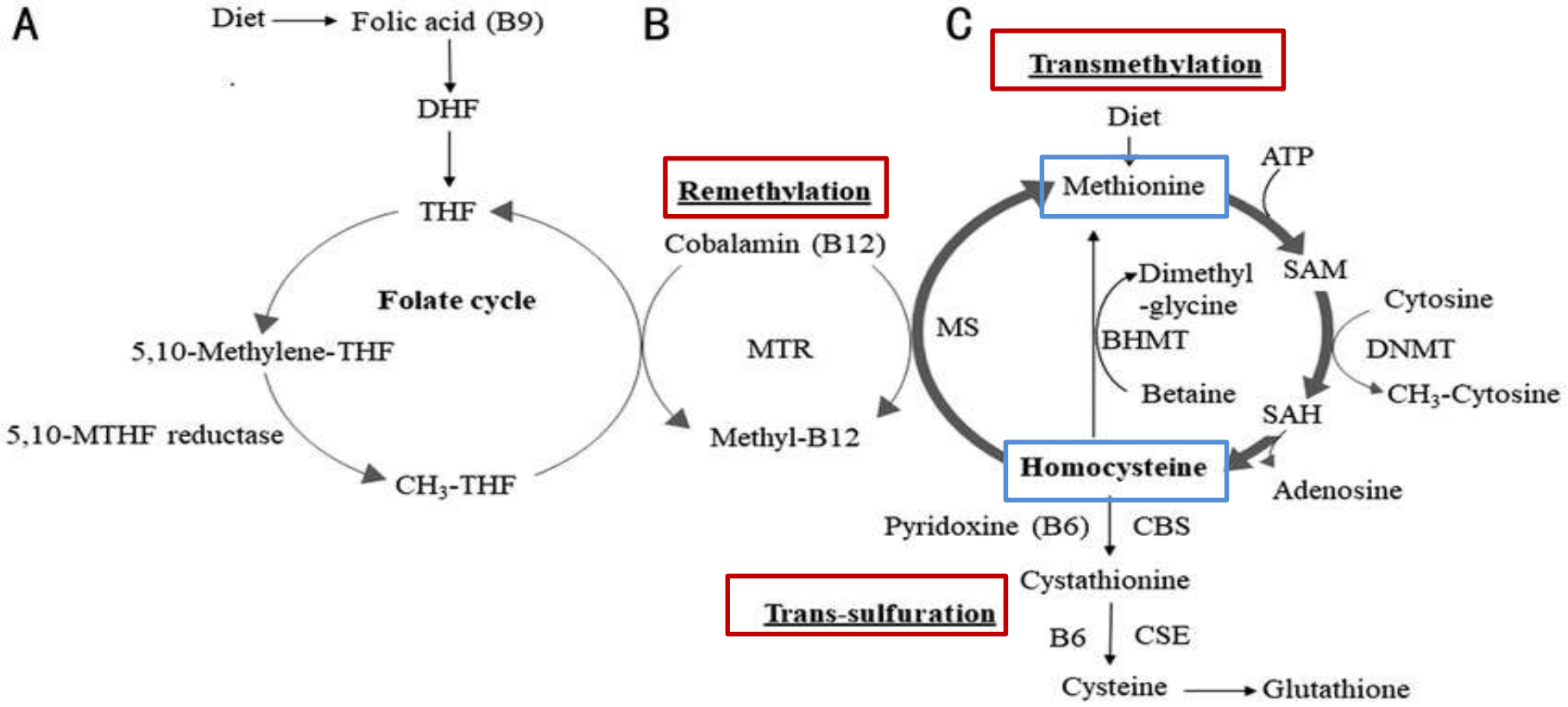
1. Aguilar *et al*., 2008.
2. Sloan, 2008
3. Scalabrino G. Subacute combined degeneration one century later. The neurotrophic action of cobalamin (vitamin B12) revisited. J Neuropathol Exp Neurol. 2001 Feb;60(2):109-20.
4. Groff J, Gropper S. Advanced Nutrition and Human Metabolism. 3rd ed. Wadsworth; 2000.

B12 Absorption

- After B12 is absorbed into the intestinal cells, it attaches to *transcobalamin II* (TC2).
- TC2 is made in the intestinal cells → through the blood and CSF → transports to all body tissues
- Once the B12-TC2 complex arrives at the cell where it is needed, B12 is released from TC2 in the form of HyCbl → then turned into AdoCbl → then MeCbl and used for their respective enzymes.



Role of Cobalamin (B12) in Methionine-Homocysteine Cycle

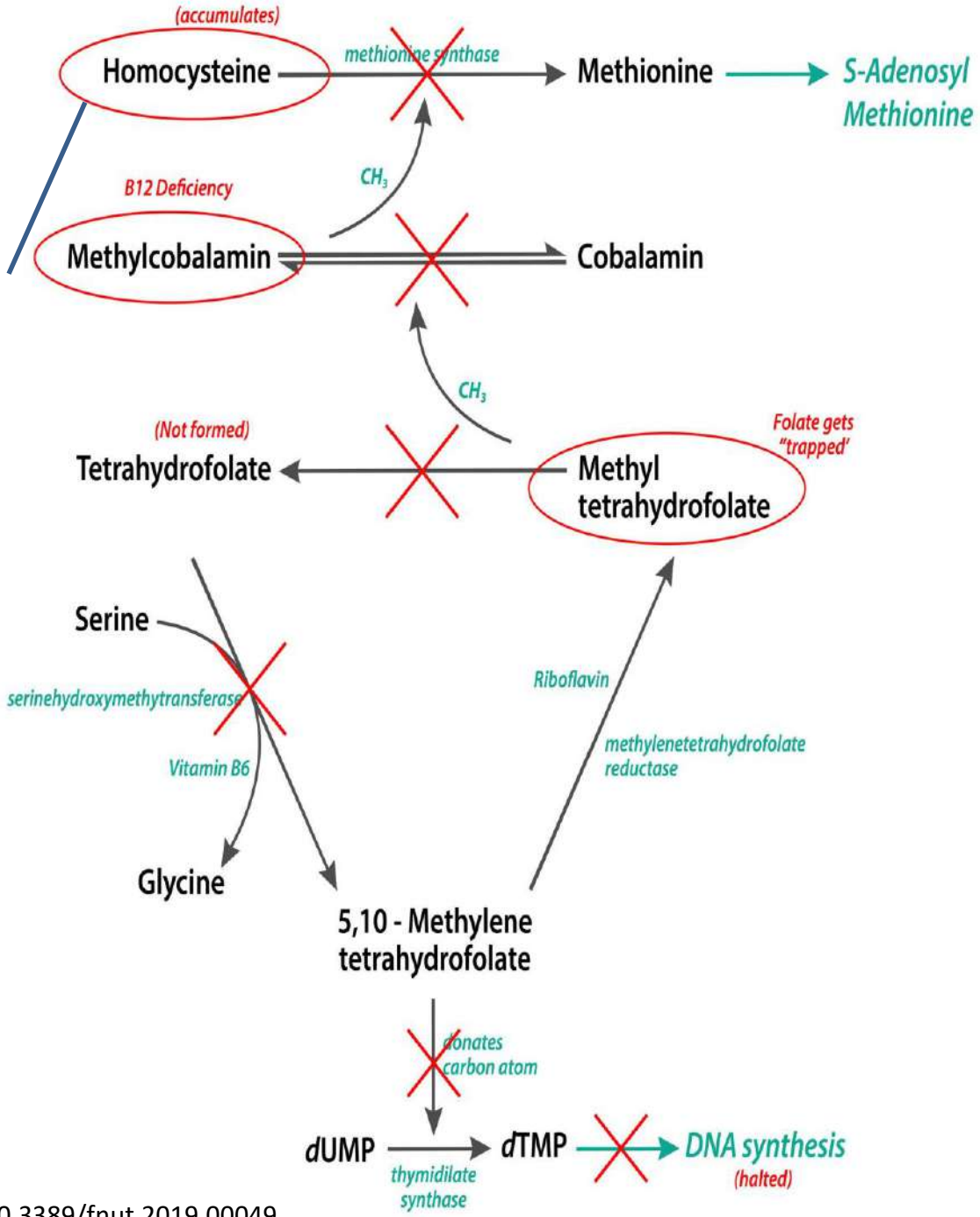


- Methylation by S-adenosylmethionine (SAM) is important for **lecithin synthesis** which is essential to repair myelin sheath damage

5. Gao, J., Cahill, C. M., Huang, X., Roffman, J. L., Lamon-Fava, S., Fava, M., Mischoulon, D., & Rogers, J. T. (2018). S-Adenosyl Methionine and Transmethylation Pathways in Neuropsychiatric Diseases Throughout Life. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*, *15*(1), 156–175.

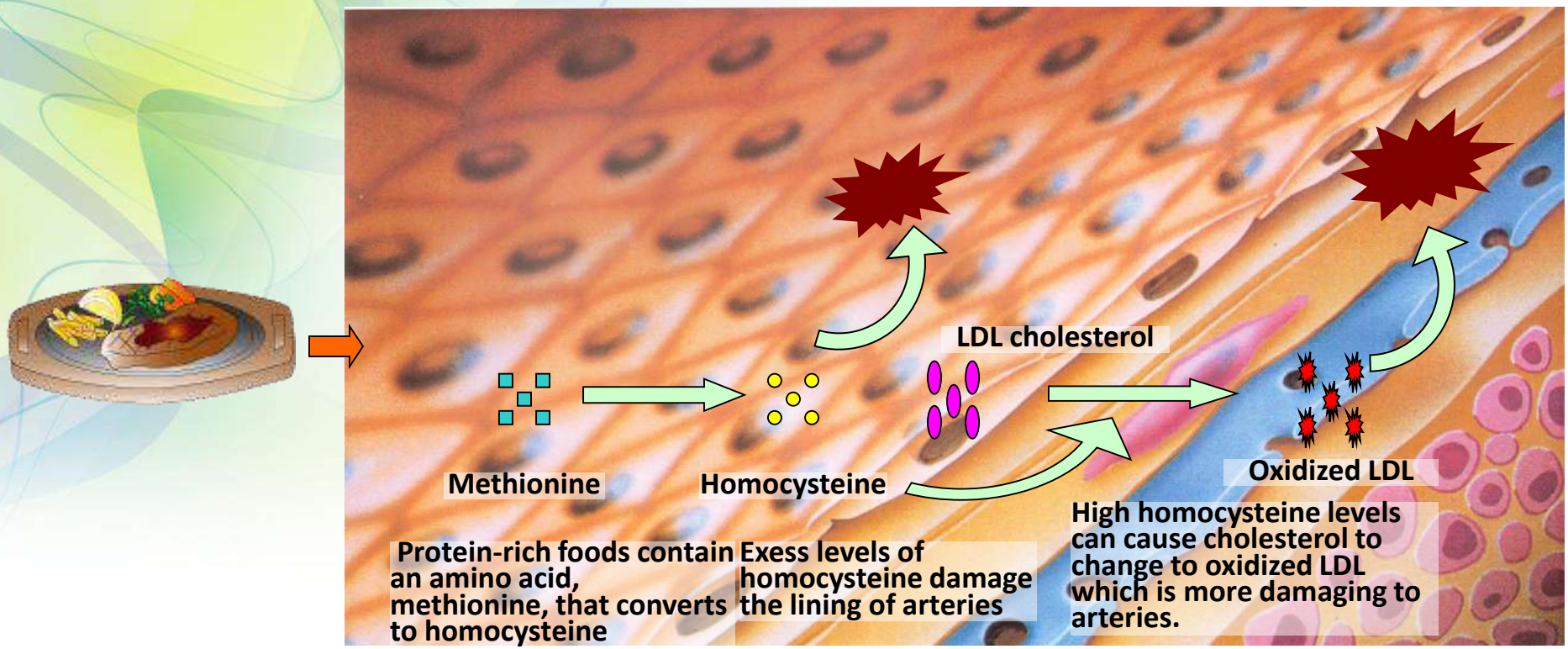
HYPERHOMOCYSTEINEMIA

Oxidative stress↑
inflammation↑
Nitric oxide ↓
Metalloproteinase↑
Collagen synthesis↑
Smooth cell proliferation↑
Foam cell↑



6. Caterina Tinelli, et al. Front. Nutr. 6:49. doi: 10.3389/fnut.2019.00049

How is a Hyperhomocysteinemia (Hhcys) harmful?



- HHcys in the blood can also cause cholesterol to change to oxidized low-density lipoprotein, which is more damaging to the arteries.
- HHCys promotes the formation of atherosclerotic plaques, atherothrombotic events through endothelial dysfunction, the enhancement of inflammation and the so called thrombophilic profile.

7. Tinelli C, et al (2019) Hyperhomocysteinemia as a Risk Factor and Potential Nutraceutical Target for Certain Pathologies. Front. Nutr. 6:49

Differentiation of Cobalamin Features

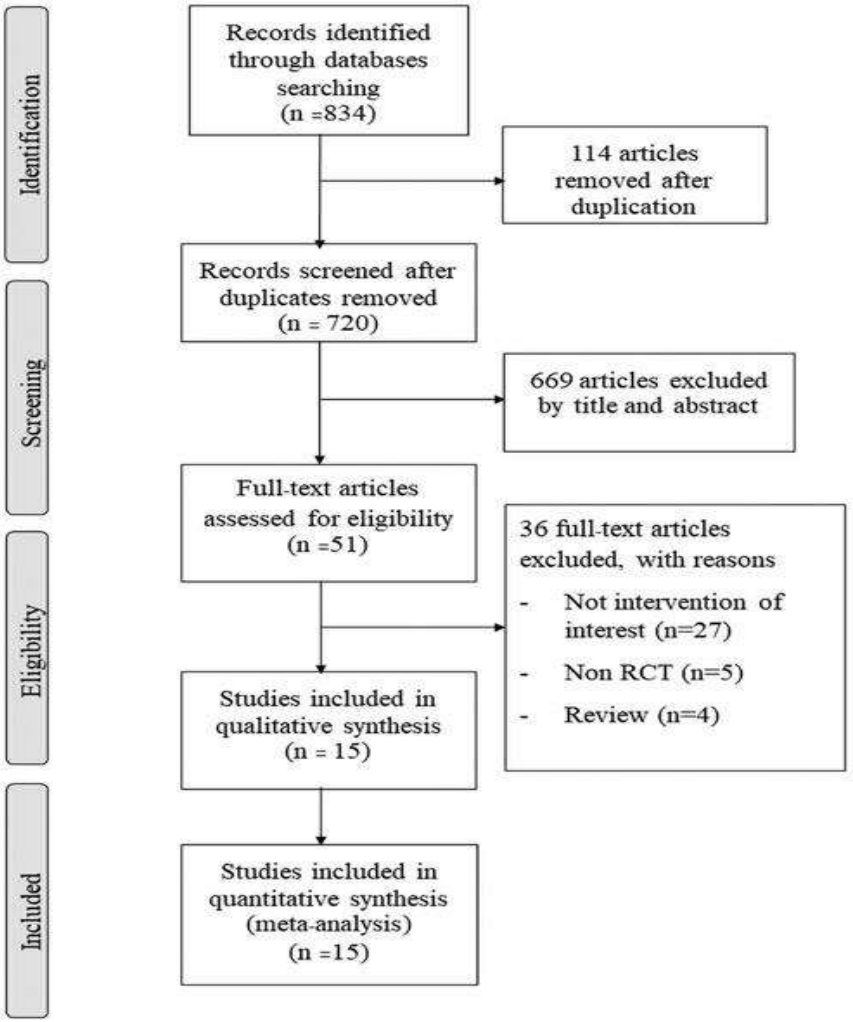
- Substitution of the cyanide (CN) side chain with methyl (CH_3) sidechain increases the neural uptake by the subcellular organelles of neurons.
- MeCbl promote myelination and transport of the axonal cytoskeleton, thereby helping to maintain and regenerate peripheral nerves.
- MeCbl promotes differentiation of Schwann cells and remyelination sciatic nerve .
- MeCbl and AdoCbl are active coenzymes form intracellularly important for normalization of hematological and neurological clinical manifestation.
- Oral Vit. B12 is as effective as parenteral supplementation.
- MeCbl is more suitable than CyCbl in patients with impaired renal function.

8. Nishimoto et al. *Front. Cell. Neurosci. 9:298. doi: 10.3389/fncel.2015.00298*)
9. Spence JD. Clin Chem Lab Med 2013; 51(3): 633–637.

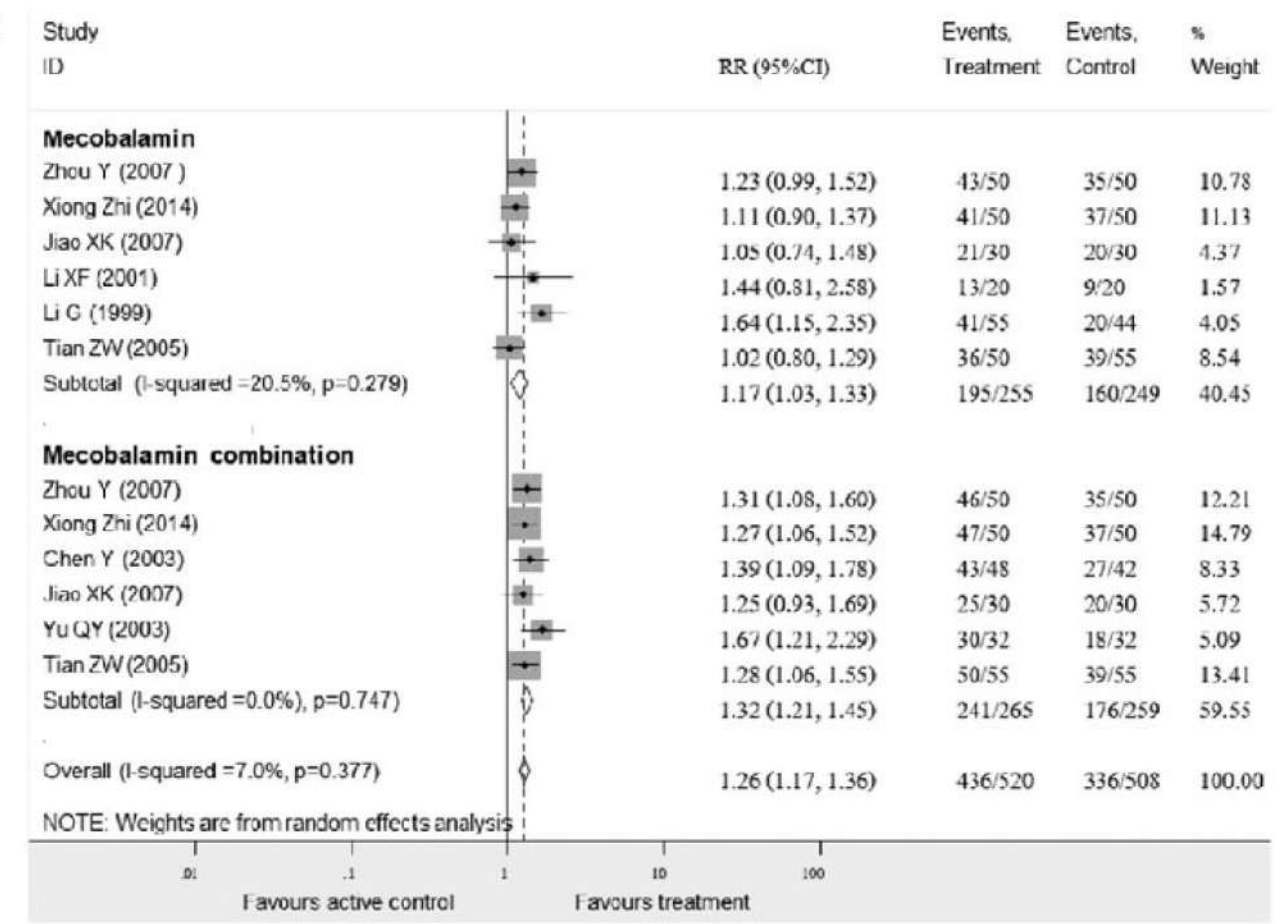
Efficacy and Safety of Mecobalamin on Peripheral Neuropathy: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Aim : To assess the efficacy and safety of MeCbl on peripheral neuropathy

Method: relevant electronic database searched on efficacy & safety of cobalamine. The clinical therapeutic efficacy, pain score, neuropathic symptom score, nerve conduction velocities (NCVs), and adverse events of MeCbl were assessed and were pooled by using a random-effects model.



10. Sawangjit et al. THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE Vol. 00, Number 00, 2020, pp. 1–13.



- MeCbl alone was more effective on peripheral neuropathy than active controls (RR 1.17; 95% CI 1.03–1.33; p 0.015).
- The proportion of patients who achieved clinical therapeutic efficacy was even higher for MeCbl combination treatment with active control.

TABLE 3. SUBGROUP ANALYSES FOR CLINICAL THERAPEUTIC EFFICACY OUTCOME

Subgroup analysis	*No. of participants (studies)*	*RR (95% CI)*	p	*Heterogeneity test* p	*Heterogeneity test* I^2, %
MC monotherapy versus active control					
Main analysis	**504 (6)**	**1.17 (1.03–1.33)**	**0.015**	**0.279**	**20.5%**
Patient types					
1. DPN	399 (5)	1.22 (1.06–1.40)	0.006	0.312	16.0%
2. PHN	105 (1)	1.02 (0.80–1.29)	0.902	—	—
Dosage forms					
1. Oral	200 (3)	1.12 (0.94–1.33)	0.198	0.634	0.0%
2. IV	100 (1)	1.23 (0.99–1.52	0.058	—	—
3. IM	105 (1)	1.02 (0.80–1.29)	0.902	—	—
3. IM then oral	99 (1)	1.64 (1.15–2.35)	0.007	—	—
Duration of treatment					
1. ≤4 weeks	345 (4)	1.14 (1.00–1.29)	0.045	0.560	0.0%
2. >4 weeks	159 (2)	1.31 (0.84–2.04)	0.237	0.073	68.9%
MC in combination of other treatments versus active control					
Main analysis	**524 (6)**	**1.32 (1.21–1.45)**	**<0.001**	**0.377**	**7.0%**
Patient types					
1. DPN	414 (5)	1.34 (1.21–1.48)	<0.001	0.474	0.0%
2. PHN	110 (1)	1.28 (1.06–1.56)	0.010	—	—
Dosage forms					
1. Oral	160 (2)	1.26 (1.09–1.47)	0.003	0.927	0.0%
2. IV	100 (1)	1.31 (1.08–1.60)	0.007	—	—
3. IM	264 (3)	1.38 (1.20–1.58)	<0.001	0.370	0.0%
Duration of treatment					
1. ≤4 weeks	464 (5)	1.33 (1.21–1.47)	<0.001	0.635	0.0%
2. >4 weeks	60 (1)	1.25 (0.93–1.69)	0.144	—	—

The main analysis with significance was shown in bold values.
CI, confidence interval; DPN, diabetic peripheral neuropathy; IM, intramuscular; IV, intravenous; MC, mecobalamin; PHN, postherpetic neuropathy; RR, risk ratio.

- According to the analyses by type of peripheral neuropathy, dosage form of mecobalamin, and duration of treatment, **mecobalamin alone and in combination is effective in patients with DPN during short-term treatment (< 4 weeks).**

Adverse events

- Safety outcomes were reported in 8 out of 15 studies with 987 patients
- The numbers of adverse events were comparable in the mecobalamin and active control groups.
- There was no report of serious adverse events or death during administration of any form of mecobalamin for one to 24 weeks.
- The most common adverse events reported in the mecobalamin (mecobalamin alone and in combination) groups were gastrointestinal symptoms (abdominal distension, 4 cases; diarrhea, 7 cases; and nausea, 5 cases), enhanced local skin redness and irritation (13 cases), edema (5 cases), and dizziness (4 cases). These adverse events were reported to be of mild severity.

Randomized Controlled Trial of the Effect of Short-term Coadministration of Methylcobalamin and Folate on Serum ADMA Concentration in Patients Receiving Long-term Hemodialysis.

Hemodialysis: Serum asymmetric dimethylarginine (ADMA) increased → **cv risk ↑**

Design: RCT, no-blinding, Folate alone (15 mg/d) in 20 pts; Folate + Methycobalamin (500 µg/post HD, 3 times weekly) in 20 pts.

Primary outcome: normalization of Hcyst level (<15 µmol/L), ADMA ↓

Results:

- The proportion showing normalization of plasma homocysteine levels was much greater in the methylcobalamin group (18 of 20 patients; 90%) than in the folate group (6 of 20; 30%; $P<0.001$).
- The percentage of decrease in ADMA levels was greater in the methylcobalamin than folate group (25.4% 10.2% vs 13.2% 11.2%; $P<0.001$).

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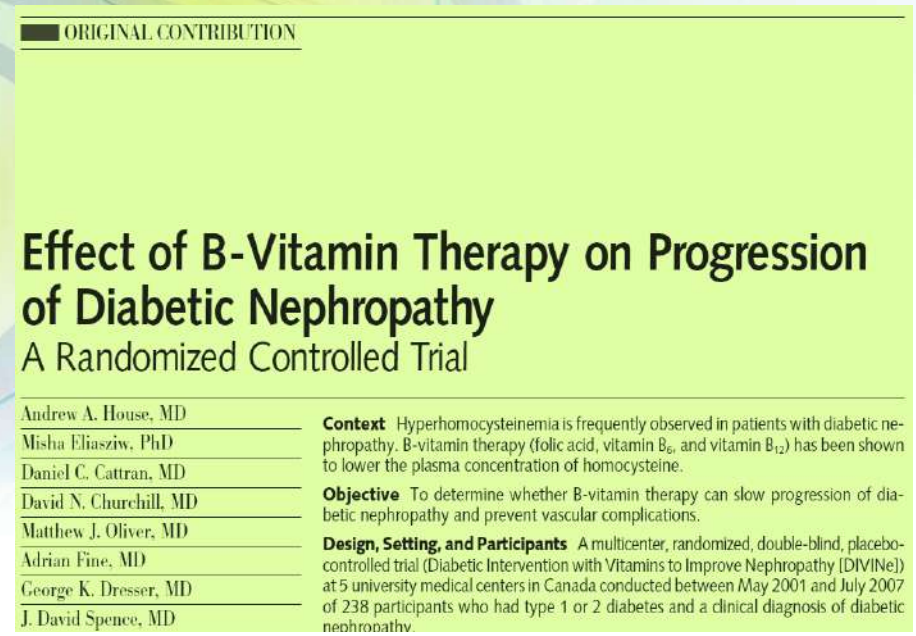
Coadministration of intravenous methylcobalamin + folate in hemodialysis patients normalized hyperhomocysteinemia and decreased ADMA levels and arterial stiffness

11. Koyama et al. American Journal of Kidney Diseases, Vol 55, No 6 (June), 2010: pp 1069-1078

Diabetic Intervention with Vitamins to Improve Nephropathy [DIVINe] Study



ORIGINAL CONTRIBUTION

Effect of B-Vitamin Therapy on Progression of Diabetic Nephropathy

A Randomized Controlled Trial

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Context Hyperhomocysteinemia is frequently observed in patients with diabetic nephropathy. B-vitamin therapy (folic acid, vitamin B_6, and vitamin B_{12}) has been shown to lower the plasma concentration of homocysteine.

Objective To determine whether B-vitamin therapy can slow progression of diabetic nephropathy and prevent vascular complications.

Design, Setting, and Participants A multicenter, randomized, double-blind, placebo-controlled trial (Diabetic Intervention with Vitamins to Improve Nephropathy [DIVINe]) at 5 university medical centers in Canada conducted between May 2001 and July 2007 of 238 participants who had type 1 or 2 diabetes and a clinical diagnosis of diabetic nephropathy.

Objective To determine whether B-vitamin therapy can slow progression of diabetic nephropathy and prevent vascular complications.

Design, Setting, and Participants A multicenter, randomized, double-blind, placebo-controlled trial at 5 university medical centers in Canada conducted between May 2001 - July 2007 of 238 participants who had type 1 or 2 diabetes and a clinical diagnosis of diabetic nephropathy.

Intervention Single tablet of B vitamins containing folic acid (2.5 mg/d), vitamin B_6 (25 mg/d), and vitamin B_{12} (1 mg/d), or matching placebo.

Main Outcome Measures Change in radionuclide glomerular filtration rate (GFR) between baseline and 36 months.

House A, et al. JAMA, April 28, 2010—Vol 303, No. 16

Table 2. Least Squares Mean Change From Baseline at Prespecified Follow-up Visits by Treatment Group From Mixed Linear Models[a]

	Overall Baseline Mean (SE) Score (n = 238)	LS Mean (SE) Change				*P* Value			Difference in LS Mean Change at 36 mo	
		12 mo (n = 111) (n = 107)	18 mo (n = 104) (n = 101)	24 mo (n = 88) (n = 83)	36 mo (n = 61) (n = 57)	Between Treatment Groups	Among Visits	Treatment × Visit Interaction	Between Groups (95% CI)	*P* Value
Radionuclide GFR										
Placebo	54.7 (1.9)		−8.1 (1.4)		−10.7 (1.7)	.045	<.001	.09	−5.8 (−10.6 to −1.1)	.02
B vitamins			−10.2 (1.4)		−16.5 (1.7)					
MDRD GFR										
Placebo	54.0 (1.8)	−5.4 (1.0)	−8.5 (1.0)	−8.7 (1.1)	−9.1 (1.2)	.26	<.001	.02	−4.4 (−7.8 to −1.0)	.01
B vitamins		−5.5 (1.0)	−8.7 (1.0)	−9.9 (1.1)	−13.5 (1.2)					
Plasma total homocysteine										
Placebo	15.5 (0.3)	1.1 (0.4)		2.1 (0.4)	2.6 (0.4)	<.001	<.001	.16	−4.8 (−6.1 to −3.7)	<.001
B vitamins		−2.7 (0.4)		−2.1 (0.4)	−2.2 (0.4)					
Proteinuria										
Placebo	1.47 (0.11)	0.25 (0.13)	0.33 (0.13)	0.21 (0.14)	0.17 (0.16)	.46	.88	.66	0.05 (−0.39 to 0.50)	.82
B vitamins		0.08 (0.13)	0.11 (0.13)	0.08 (0.14)	0.22 (0.16)					
MMSE score[b]										
Placebo	28.7 (0.12)	−0.08 (0.11)		−0.49 (0.12)	−0.12 (0.14)	.82	.38	<.001	−0.28 (−0.67 to 0.11)	.15
B vitamins		−0.20 (0.11)		0.01 (0.12)	−0.40 (0.14)					

Results

- Radionuclide GFR decreased by a mean (SE) of 16.5 (1.7) mL/min/1.73 m_2 in the B-vitamin group compared with 10.7 (1.7) mL/min/1.73 m_2 in the placebo group (95% [CI], −10.6 to −1.1; *P*=.02).
- Plasma total homocysteine decreased by a mean (SE) of 2.2 (0.4) µmol/L at 36 months in the B-vitamin group compared with a mean (SE) increase of 2.6 (0.4) µmol/L in the placebo group (95% CI, −6.1 to −3.7; *P*.001, in favor of B vitamins).

12. House A, et al. JAMA, April 28, 2010—Vol 303, No. 16

- Participants randomized to receive B vitamins had a significantly greater number of cardiovascular and cerebrovascular events.
- The 36-month risk of a composite outcome, including MI, stroke, revascularization, and all-cause mortality, in the B-vitamin group was double that in the placebo group (HR, 2.0; 95% CI, 1.0-4.0; *P*=.04)

Table 3. Kaplan-Meier 36-Month Risk of Outcomes and Hazard Ratios From Cox Proportional Hazards Regression Model[a]

Outcomes	Outcomes, No. (%)		Hazard Ratio (95% CI)	*P* Value
	Placebo Group (n = 119)	B-Vitamin Group (n = 119)		
Secondary outcomes				
Dialysis	10 (11.7)	10 (12.3)	1.1 (0.4-2.6)	.88
MI	4 (4.6)	8 (7.8)	2.1 (0.6-6.9)	.23
Stroke	1 (1.3)	6 (7.2)	6.6 (0.8-54.4)	.08
Revascularization	5 (6.1)	7 (6.3)	1.5 (0.5-4.6)	.51
All-cause mortality	6 (6.6)	7 (6.7)	1.2 (0.4-3.6)	.72
MI, stroke, revascularization, all-cause mortality	13 (14.4)	24 (23.5)	2.0 (1.0-4.0)	.04
Tertiary outcomes				
MI, stroke, all-cause mortality	10 (10.8)	20 (20.1)	2.2 (1.0-4.6)	.046
Amputation	1 (1.6)	2 (2.1)	2.1 (0.2-23.2)	.54

Abbreviations: CI, confidence interval; MI, myocardial infarction.
[a] Revascularization indicates peripheral and cardiac angioplasty and cardiac bypass procedures. Amputation indicates amputation for peripheral vascular disease.

in this RCT , participants with diabetic nephropathy and stages 1 - 3 CKD, the use of high doses of B vitamins (containing 2.5 mg/d of folic acid, 25 mg/d of vitamin B6, and 1 mg/d of vitamin B12) compared with placebo resulted in **a greater decrease in GFR** and **an increase in MI and stroke**

12. House A, et al. JAMA, April 28, 2010—Vol 303, No. 16

Diabetic Intervention with Vitamins to Improve Nephropathy (DIVINe) study

- Combination of folic acid 5 mg, pyridoxine 25 mg and cyanocobalamin 1000 µg not only accelerated the decline of renal function, but also significantly increased cardiovascular events.
- Analyses in response to letters to the editor revealed that all the events occurred in patients with a baseline GFR < 50 mL/min/1.73 m2.

12. House, A. A, et al. (2010). *Effect of B-Vitamin Therapy on Progression of Diabetic Nephropathy. JAMA, 303(16), 1603.*

Potential Mechanisms of MeCbl Efficacy

- Accelerating transmethylation in nerve tissues, increasing myelination.
- Promoting conversion of homocysteine to methionine, decreasing oxidative stress and advanced glycosylated end-products
- Correction of impaired neural signaling of protein kinase C (the main pathophysiology of DPN).[15,16]
- MeCbl also acts directly on the neuron and has a more rapid onset of action than other forms of B vitamin.[21]

13. Thakkar K, Billa G. Treatment of vitamin B12 deficiencymethylcobalamine? Cyancobalamine? Hydroxocobalamin?- clearing the confusion. Eur J Clin Nutr 2015;69:1–2.
14. Group AL. ALSUntangled No. 30: Methylcobalamin. Amyotroph Lat Scl Front Degen 2015;16:536–539.
15. Zhang M, Han W, Hu S, Xu H. Methylcobalamin: A potential vitamin of pain killer. Neural Plast 2013;2013:6.


Thank You

SERTIFIKAT

Diberikan kepada

Dr. Med. dr. Abraham Simatupang, M.Kes, Sp.S

sebagai

Speaker

SIMPOSIUM VIRTUAL

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