Comparative Bioavailability and Utilization of Particular Forms of B_{12} Supplements With Potential to Mitigate B_{12}-related Genetic Polymorphisms

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Abstract

Context: Three natural forms of vitamin B_{12} are commercially available: methylcobalamin (MeCbl), adenosylcobalamin (AdCbl), and hydroxycobalamin (OHCbl), all of which have been shown in clinical studies to improve vitamin B_{12} status. They are bioidentical to the B_{12} forms occurring in human physiology and animal foods. In contrast, cyanocobalamin (CNCbl), a synthetic B_{12} compound used for food fortification and in some supplements, occurs only in trace amounts in human tissues as a result of cyanide intake from smoking or other sources.

Objective: This study had 3 objectives: (1) To summarize and compare assimilation pathways for 4 B_{12} forms; (2) to determine whether supplementation with a particular B_{12} form (or combination of forms) presents any advantages for the general population or for individuals with single nucleotide polymorphisms (SNPs) in B_{12}-related pathways; and (3) to address misconceptions regarding B_{12} forms, methylation pathways, and various SNPs reported in commercially available tests.

Design: PubMed was systematically searched for articles published up to June 2016 using specific key words. Human, animal, and in vitro studies that were published in English, French, and German were included. Other studies considered were found by selecting in PubMed the suggested "related studies" and also some referenced studies.

Setting: The study occurred in Los Angeles, CA, USA.

Results: The studies reviewed provide evidence that all supplemental or food-derived B_{12} forms are reduced to a core cobalamin molecule, which converts to the intracellular active forms: MeCbl and AdCbl, in a ratio not influenced by the form of B_{12} ingested. The methyl and adenosyl components of supplemental MeCbl and AdCbl are cleaved inside cells and are not used in the synthesis of intracellular MeCbl and AdCbl, respectively. However, the overall bioavailability of each form of supplemental B_{12} may be influenced by many factors such as gastrointestinal pathologies, age, and genetics. Polymorphisms on B_{12}-related pathways may affect the efficiency of absorption, blood transport, cellular uptake, and intracellular transformations.

Conclusions: Supplementing with any of the nature bioidentical forms of B_{12} (MeCbl, OHCbl, and/or AdCbl) is preferred instead of the use of CNCbl, owing to their superior bioavailability and safety. For the majority of the population, all B_{12} forms may likely have similar bioavailabilities and physiological effects; thus, it makes sense to employ the least-expensive form of B_{12}, such as MeCbl. Individuals with particular single nucleotide polymorphisms (SNPs) affecting B_{12} assimilation may raise their B_{12} status more efficiently with 1 or more particular forms of vitamin B_{12}. However, because those types of SNPs are not currently reported in commercial tests, individuals may require either a trial-and-error approach by supplementing with 1 particular form of B_{12} at a time, or they might simply use a supplement with a combination of all 3 naturally occurring forms of B_{12} that are commercially available for a better chance of achieving faster clinical results. That approach may or may not offset genetic polymorphisms involving B_{12} metabolism and related pathways.

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The synthetic form of supplemental vitamin B_{12} has long been available in the form of cyanocobalamin (CNCbl), both for oral and injectable use. Subsequently, the naturally occurring forms of B_{12}—methylcobalamin (MeCbl), adenosylcobalamin (AdCbl), and hydroxycobalamin (OHCbl)—have been made available, and they seem conceptually preferable because they are bioidentical to the B_{12} forms occurring in human physiology and animal foods. In contrast, cyanocobalamin (CNCbl), a synthetic B_{12} compound used for food fortification and in some supplements, occurs only in trace amounts in human tissues as a result of cyanide intake from smoking or other sources. However, CNCbl continues to be used for food fortification and in some supplements, probably owing to its low cost and heat stability.

This literature review attempts to answer the following question: Which of the 4 forms of B_{12} commercially available today is the best to use for particular clinical cases, and should genetic polymorphisms involved with B_{12}-related pathways be guiding the selection for a particular use?

A few studies have been performed to evaluate and compare the bioavailability and metabolic pathways of various forms of vitamin B_{12}. Unsubstantiated marketing of B_{12} supplements often claim that their clinical effects depend on the B_{12} form(s) they contain, and some claims have promoted the marketing of certain forms of supplemental B_{12}, including that supplemental MeCbl may be superior to other forms in supporting intracellular methylation reactions, that supplemental AdCbl may be better at increasing intramitochondrial levels of AdCbl, or that supplemental OHCbl may result in lower levels of *S*-adenosylmethionine (SAMe) than supplemental MeCbl. These claims are based on unsubstantiated links between metabolic pathways and particular genetic mutations.

In the current literature review, the research team evaluated whether the results of the reviewed studies provide evidence of the effects of B_{12}-related polymorphisms, as reported in currently available commercial tests, to be modulated in some novel way by supplementing diet with particular forms of B_{12}.

Methods

PubMed was systematically searched for articles published up to June 2016 using the following key words or associations: *vitamin B_{12}* OR *cobalamin* OR *adenosylcobalamin* OR *cyanocobalamin* OR *hydroxycobalamin* OR *methylcobalamin* AND *metabolism* OR *absorption*; *cobalamin* AND *methylmalonic acidemia* OR *homocystinuria* OR *homocysteine* OR *methylmalonic acid*. Human, animal, and in vitro studies published in English, French, and German were included. Other studies considered were found by selecting in PubMed the suggested "related studies" and also some referenced studies.

Results

Vitamin B_{12} Forms

Bioavailability of CNCbl, Naturally Occurring Forms of B_{12}, and Pseudo-B_{12} Corrinoids. The term *vitamin B_{12}* includes a number of chemical compounds with vitamin-B_{12} activity in humans, and those compounds contain a common corrinoid group, centered on the mineral cobalt and various ligands, such as cyano, methyl, adenosyl, and hydroxyl ligands.

Although MeCbl, AdCbl, and OHCbl are bioidentical to the B_{12} forms occurring in human physiology and animal foods and CNCbl occurs only in trace amounts in human tissues as a result of cyanide intake from smoking or other sources, all B_{12} forms have been shown in clinical studies to improve vitamin B_{12} status.[1-6] The CNCbl form needs to be broken down to cobalamin and cyanide to be converted to the active forms of B_{12} in human physiology. That reaction may not be efficient in individuals with SNPs on B_{12} metabolic pathways.[2] That difficulty is not surprising because the CNCbl form of B_{12} is not part of normal human physiology.

One animal study compared the effects of supplementation with MeCbl versus CNCbl and showed that CNCbl urinary excretion that was 3 times higher than that of MeCbl. Although absorption in the blood of the 2 B_{12} forms was similar, the study found that MeCbl supplementation caused 13% more cobalamin to be stored in the liver than did CNCbl supplementation.[7]

Chalmers[8] reviewed the results of 3 human studies that also found lower tissue retention of B_{12} as a result of supplementation with CNCbl rather than OHCbl, MeCbl, or AdCbl, together with increased urinary excretion of CNCbl. The researchers concluded that the lower bioavailability of CNCbl was due to its lower efficiency in cellular uptake and metabolic activation. Other researchers are concerned about cyanide accumulation in human tissues from long-term intake of CNCbl from supplements and/or fortified foods.[2,9] Thus, it seems that the CNCbl is an inferior choice for use in nutritional supplements or injections of B_{12}. In fact, a *Lancet* review has proposed the discontinuation of CNCbl because OHCbl had been made available, and owing to concerns regarding the cyanide moiety, especially for smokers.[10]

Vitamin B_{12} is synthesized by particular bacteria, such as *Propionibacterium freudenreichii* sbsp *shermanii*, or certain strains of lactobacilli, such as *Lactobacillus lechmanii*. Other than in certain algae, vitamin B_{12} is absent from most plant foods, unless they have been fermented. Bacteria produce various forms of B_{12}, of which only a few are bioavailable in human physiology.

The amount of B_{12} synthesized by human intestinal flora is negligible and unlikely to be absorbed because it is produced in the colon. Animals store bioavailable vitamin B_{12} compounds in their milk, eggs, muscles and organs, and especially in the liver.[11] AdCbl is the predominant B_{12} form found in meats, at 68%, with the rest occurring as OHCbl and MeCbl.[12] MeCbl is the predominant form in milk and eggs.

Many vegetarian sources of B_{12}—such as fermented foods, algae, seaweed, spirulina, yeast, and mushrooms—may not be bioavailable, despite claims on B_{12} labels.[13] A large portion of the assayed vitamin B_{12}–like compounds have no B_{12} activity in human physiology and are referred to as pseudo-B_{12} corrinoids. They compete on blood transport proteins with bioavailable B_{12} forms, thus further aggravating B_{12} deficiency. Vitamin B_{12} deficiency in vegetarians is significant at 62%, 25% to 86%, 21% to 41%, and 11% to 90% in pregnant women, children, adolescents, and older individuals, respectively.[11,14] However, those estimates are based on recommended dietary allowance (RDA) guidelines, which are often inadequate, as is discussed in the next section.

B_{12} Recommended Dietary Allowance Versus Recommendations for Optimal B_{12} Intake Based on Other Scientific Criteria. The RDA of vitamin B_{12} for adults is set at 2.4 μg/day in the United States.[15] The RDA guidelines state that 10% to 30% of adults older than 50 years often have B_{12} malabsorption syndromes, driving absorption rates as low as 1% of the ingested B_{12}. Thus, those adults would need to ingest 240 μg of B_{12} to absorb at least 2.4 μg.[15]

However, a 2010 study assessed B_{12} status versus B_{12} intake by measuring homocysteine and methylmalonic acid and concluded: "In persons with normal absorption, our data indicate that an intake of 4–7 μg of vitamin B_{12}/d is associated with an adequate vitamin B_{12} status, which suggests that the current RDA of 2.4 μg of vitamin B_{12}/d might be inadequate for optimal biomarker status, even in a healthy population between 18 and 50 years of age."[16]

Optimal intake of B_{12} has been recommended at 7 μg by Fenech[17] based on the support of optimizing DNA replication, or at 17.6 μg by Cordain,[18] based on average B_{12} intakes during the evolution of humans.

Comparison of B_{12} Forms: Absorption and Blood Transport

Vitamin B_{12} occurs in foods bound in a protein matrix, from which it needs to be liberated during digestion, unlike B_{12} added as fortification. The bioavailability of food-derived B_{12} depends on adequate chewing and on the levels of stomach acid and proteolytic enzymes. After liberation from the food matrix, B_{12} binds to haptocorrin (HC), also called R factor, which is a protein secreted in the saliva and stomach fluids and which carries B_{12} along the gastrointestinal tract. Subsequently, proteolytic enzymes are needed to liberate B_{12} from HC to make it available for 2 distinct routes of absorption, either (1) binding to the intrinsic factor (IF) protein or (2) being taken into the gastrointestinal mucosa by diffusion. IF facilitates B_{12} absorption by the endocytosis route in the ileum, but it gets saturated at the level of 2 μg of B_{12} per meal.

All conditions that involve impaired production of IF, such as autoimmune pernicious anemia or atrophic gastritis, and/or a compromised intestinal absorptive function, as in celiac disease, ulcerative colitis, Crohn's disease, or tropical sprue, may greatly impair B_{12} absorption by endocytosis.

Fortunately, absorption of B_{12} by diffusion bypasses the need for IF, but it only occurs when driven by a concentration gradient with B_{12} doses much higher than those naturally found in food.[19,20] One study evaluated absorption rates of CNCbl when given at escalating doses.[1] The results revealed various absorption rates of B_{12} based on dose level: (1) 50% for doses <0.5 μg, (2) 20% for doses of approximately 1 μg, and (3) only 1% to 1.2% for doses of approximately 500 μg. It was estimated that 10 to 12 μg of B_{12} may be absorbed from a dose of 1000 μg. A human study showed similar absorption rates for CNCbl versus those of OHCbl at such doses as 100 μg, 500 μg, and 1000 μg.[21] CNCbl absorption was also found to be similar to that of MeCbl in an animal study.[7]

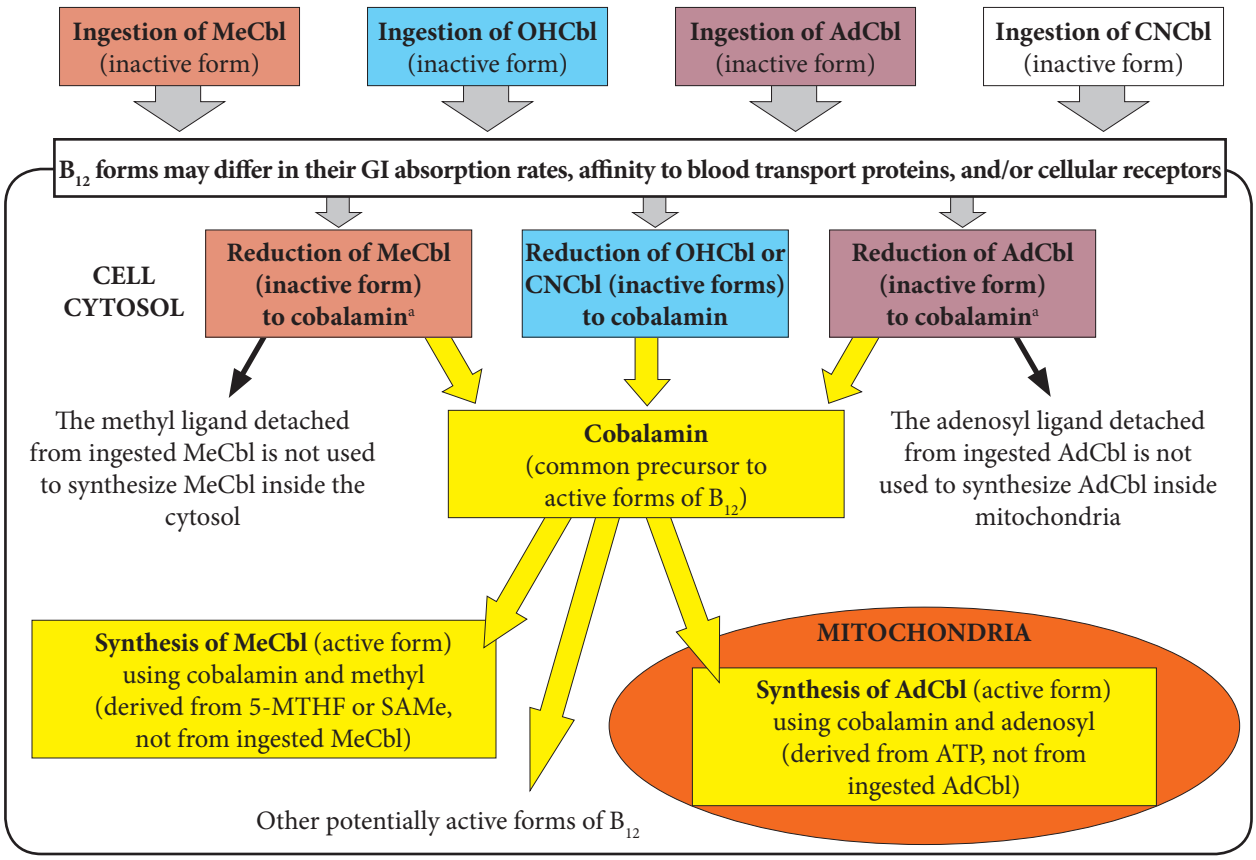
Unlike vitamin B_{12} found in food, supplemental B_{12} is not bound to protein; therefore, it readily binds to HC, and it is also available for direct absorption by diffusion. The supplement's delivery system may be a sublingual lozenge, a liquid, or a capsule or tablet that is meant to open up in the stomach or lower intestinal tract. It is not clear if or how much absorption occurs by the oral mucosa route owing to inadequate studies comparing sublingual with encapsulated B_{12}.[3,4] The sublingual formulations may achieve partial absorption directly through the oral mucosa, but it is conceivable that part of the B_{12} may be bound by HC immediately in the saliva and then carried down to be absorbed in the GI tract by IF or by diffusion. B_{12} bioavailability from a nutritional supplement is not impaired in cases of low stomach acidity.

All forms of B_{12} that are absorbed in the blood are transported by transcobalamin-I (TC-I) and transcobalamin-II (TC-II).[5] One study observed that AdCbl seems to be the preferred form for binding to TC-II, whereas MeCbl is bound by both TC-II and TC-I.[22] Because only TC-II delivers B_{12} inside cells, owing to specialized receptors, it appears that the AdCbl form of B_{12} may be delivered more efficiently to body cells than the MeCbl form.

Intracellular Conversions to Active Forms of B_{12}. Two forms of B_{12}, MeCbl and AdCbl, are recognized as active forms of B_{12} in human and animal physiology because they act as cofactors in important metabolic reactions. However, numerous studies have shown that those forms of B_{12} are not retained intact in their active form when they are ingested from foods or supplements because they go through intracellular metabolism.[2,23,24] For example, a 2015 comprehensive review of vitamin B_{12} metabolism stated that no advantage was demonstrated in using one of the B_{12} forms over another, except one related to cost.[6]

Numerous studies and reviews of B_{12} metabolism have shown that CNCbl, MeCbl, OHCbl, and AdCbl are reduced to the core cobalamin molecule inside the cytosol. It is important to note that the ligands specific to the ingested B_{12} form—methyl and adenosyl—are removed during that process and not used inside cells during the conversion of cobalamin to the 2 active forms

Figure 1. Genetic SNPs May Affect Various Steps in B_{12} Absorption, Blood Transport, and/or Conversions to Intracellular Active Forms of B_{12}



Note: The figure was adapted from Obeid et al,[6] Chu et al,[25] Gherasim et al,[26] and Quadros.[30]

[a]B_{12} is converted to cobalamin at different rates among B_{12} forms using enzymes specialized for their particular ligand.

Abbreviations: SNPs, single nucleotide polymorphisms; MeCbl, methylcobalamin; AdCbl, adenosylcobalamin; OHCbl, hydroxylcobalamin; CNCbl, cyanocobalamin; GI, gastrointestinal; SAMe, *S*-adenosylmethionine; ATP, adenosine triphosphate.

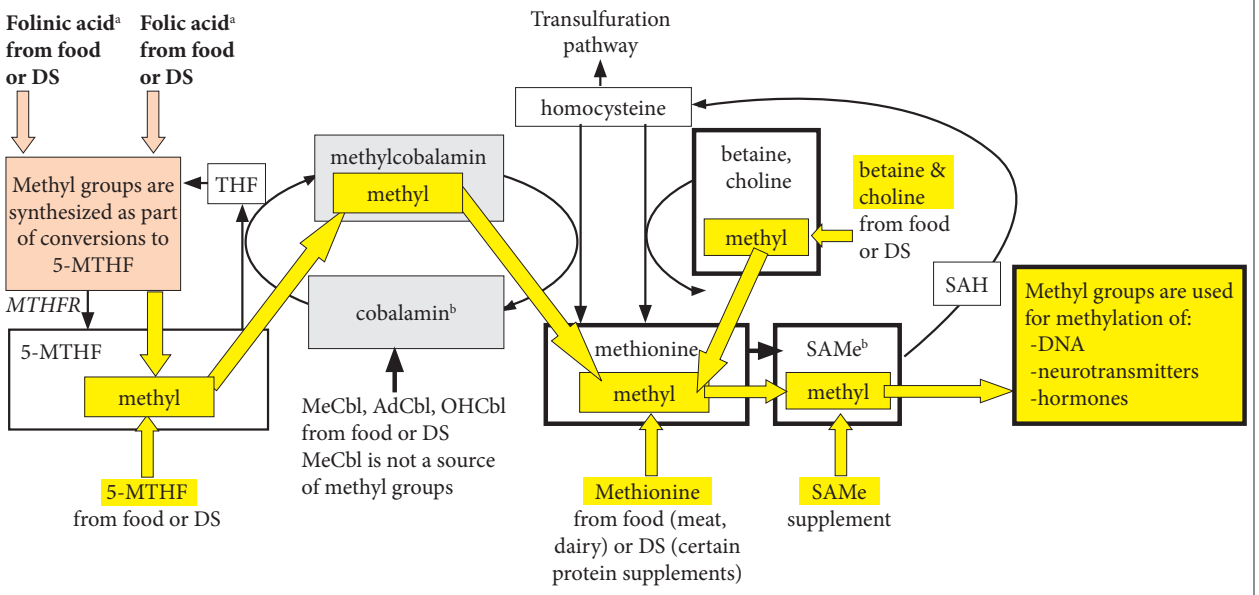
of B_{12} (Figure 1).[6,25-30] Activation of cobalamin occurs in very specific cellular environments; cobalamin is converted into MeCbl inside the cytosol and to AdCbl inside mitochondria. The final amounts and ratios of MeCbl and AdCbl produced do not depend on the initial form of B_{12} that had entered the cells.[25] However, those amounts might vary based on cell type, specific cellular conditions, and genetic polymorphisms of those metabolic pathways.

Cytosolic Methylation Reactions and Formation of MeCbl. Inside the cytosol, a portion of available cobalamin participates in cyclic methylation reactions by acquiring the methyl group from 5-methyl-folate or occasionally from SAMe (every 2000 cycles), thus being converted to MeCbl. Subsequently, MeCbl donates its methyl group to homocysteine, thereby converting it to methionine (Figure 2) while being reduced back to cobalamin.

A cellular study has clarified that the methyl group brought inside cells by supplementation with MeCbl is not used in any methylation reactions and that supplementation with that form of B_{12} does not produce more methionine as compared with supplementation OHCbl.[25] The authors stated:

> Once released from the lysosomes, both MeCbl and OHCbl were converted in the same proportions to coenzyme forms, suggesting equivalent entry into common cellular pools of cobalamin from which active forms are synthesized. All evidence supported the concept that the active MeCbl on methionine synthase in human cells forms de novo on the enzyme. Exogenous MeCbl enjoyed no advantage in binding to methionine synthase, in promoting synthesis of MeCbl, or in supporting cell division. It appeared unlikely that therapeutic MeCbl would have any advantage over OHCbl in the treatment of MeCbl deficiency or cobalamin deficiency in general.[25]

Figure 2. Sources of Methyl Groups From Diet or Supplements



Note: Dietary MeCbl is not a methyl donor. All direct and indirect sources of methyl groups from diet and supplements are highlighted in yellow. The figure was adapted from Randaccio et al[32] and Anderson et al.[33]

[a]Folinic and folic acids are indirect sources of methyl groups because they promote methyl-group synthesis during their conversions to 5-MTHF.
[b]When cobalamin is oxidized, it uses SAMe as a methyl donor, which enables it to re-enter the methylation cycles.

Abbreviations: DS, dietary supplements; THF, tetrahydrofolate; MTHFR, methyl tetrahydrofolate reductase; SAH, S-adenosyl-homocysteine; SAMe, *S*-adenosylmethionine; MeCbl, methylcobalamin; AdCbl, adenosylcobalamin; OHCbl, hydroxylcobalamin.

Another cellular study showed that the lysosomal reduction to cobalamin, when B_{12} is supplemented as AdCbl, was 67 times slower than the reduction of MeCbl to cobalamin. Thus, AdCbl supplementation may result in a slower synthesis of intracellular AdCbl and MeCbl compared with MeCbl supplementation.[31]

The methionine produced in those cyclic methylation reactions supports production of SAMe, which acts as a methyl donor in reactions involving DNA and certain hormones or neurotransmitters.[32,33] Intracellular synthesized SAMe derives its methyl component either from 5-methyl-tetrahydrofolate, with cobalamin acting as an intermediate carrier of the methyl group, or from intake of methionine, betaine, or choline. Thus, intracellular levels of SAMe are not influenced by the form of B_{12} ingested.

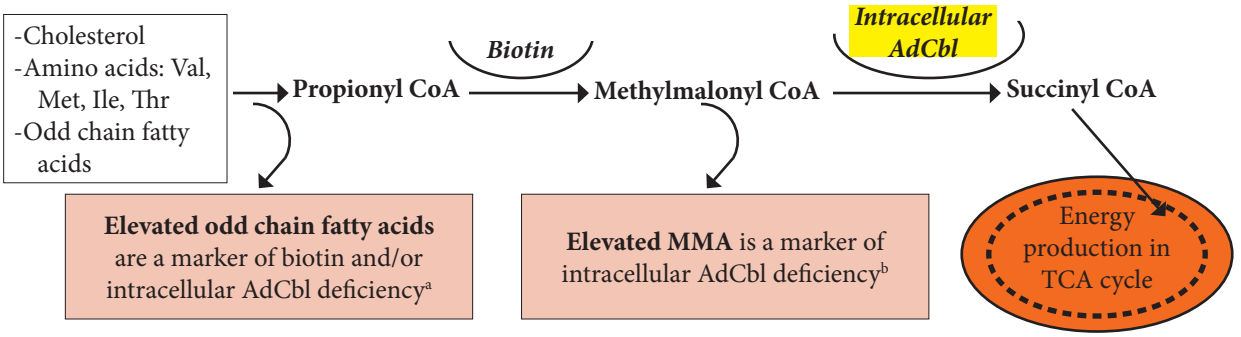
It is clear that the form of B_{12} entering the body does not differentially influence the metabolite levels in any methylation reactions. However, the amount of vitamin B_{12} ingested at one time and its bioavailability, reflected by the portion converted to cobalamin inside cells, is relevant. Those factors can influence the extent to which 5-MTHF, available inside cells, will be used for methylation reactions and DNA synthesis.[32,33]

Mitochondrial Metabolism Related to AdCbl. Inside the mitochondria, a portion of available cobalamin is converted to AdCbl, a cofactor for the conversion of methylmalonyl CoA (MMCoA) to succinyl-CoA, which enters the Krebs cycle. Figure 3 illustrates the metabolites that typically convert to MMCoA and that are further converted to energy if AdCbl levels are adequate.[22]

All B_{12} forms are converted to AdCbl, because they are all broken down to cobalamin first while the adenosyl group that is used to assemble AdCbl is synthesized from adenosine triphosphate inside the mitochondria.[26,29] Consequently, if supplemental B_{12} is in the AdCbl form, it is unlikely that the total AdCbl produced inside the mitochondria would be higher compared with that derived from other supplemental B_{12} forms.[6]

Newly Discovered Roles for B_{12} as an Active Cofactor in Nitric Oxide Metabolism. Glutathionyl-cobalamin (GSHCbl) is an intermediate in cobalamin metabolism. GSHCbl is a newly proposed active form of B_{12}, a cofactor affecting nitric oxide production, protection, and action in reactions associated with cell membranes.[34,35] Those effects may have profound implications for vascular and immune health, but the results of those studies are preliminary.[36-39]

Figure 3. Mitochondrial Role of Vitamin B_{12}



Note: The figure was adapted from Beedholm-Ebsen.[22]

[a]Odd chain fatty acids are measured in the blood and may be part of essential-fatty-acid profiles in plasma or RBCs.
[b]MMA may be measured in blood or urine.

Abbreviations: Val, valine; Met, methionine; Ile, isoleucine; Thr, threonine; AdCbl, adenosylcobalamin; CoA, coenzyme A; MMA, methylmalonic acid; TCA, tricarboxylic acid; RBCs, red blood cells.

Supplementation with AdCbl has been shown to modulate the immune response by downregulating excess inflammatory processes that are mediated by inducible nitric oxide.[37] That fact may explain why B_{12} supplementation has been shown to reduce the severity of autoimmune conditions, such as rheumatoid[40] and atopic dermatitis.[41] It is likely that all forms of B_{12} may have those effects, because they are all converted to intracellular GSHCbl.

B_{12} Assimilation-related Genetic Polymorphisms

Genetic polymorphisms related to vitamin B_{12} assimilation are thought to be responsible for a difficulty optimizing B_{12} status in certain individuals, despite their adequate intake from food and/or supplemental B_{12}.[6,26,31,42-47] Figure 1 illustrates a multitude of metabolic steps where genetic polymorphisms (SNPs) might impair B_{12} absorption, blood transport, cellular uptake, and intracellular conversion to active forms.

Each B_{12} form is chaperoned out of lysosomes into the cytosol by specific proteins and then converted to cobalamin by enzymes specific to each B_{12} form. Thus, it is conceivable that individuals with SNPs on those particular metabolic pathways may benefit from supplementation with the B_{12} forms that are metabolized on the alternate pathways, if those are SNP free. However, at the time of this review, those types of SNPs are not reported in commercially available tests. In addition, no studies have proven that the effects of particular SNPs can be modulated by any particular form(s) of B_{12}.

Discussion

Based on the research available on the relative bioavailability and metabolism of the 4 commercially available forms of B_{12} that has been discussed in the current review, the following may be concluded.

All forms of B_{12}—CNCbl, MeCbl, OHCbl, and AdCbl—seem to be absorbed with similar efficiency in the blood stream but differ in overall bioavailability, as reflected by their tissue retention rates. That fact may be due to different affinities for the blood-transport binding proteins, cell receptors for B_{12} uptake, and intracellular enzymes involved in their conversion to intracellular cobalamin. All of the B_{12} forms are reduced to the core cobalamin molecule inside the cytosol and then converted to the 2 active forms of B_{12}—MeCbl and AdCbl—irrespective of the form of B_{12} ingested. It is important to understand that the conversions to active B_{12} forms do not employ the methyl or adenosyl ligand from supplemental MeCbl or AdCbl, respectively. The methyl group is derived from other molecules—5-MTHF, SAM-e, or betaine—while the adenosyl group is synthesized inside cells.

As a result, the form of ingested B_{12} may influence how much cobalamin is produced inside cells but not how it is converted to MeCbl, AdCbl, or various active metabolites involved in methylation reactions. Genetics may affect the activity of enzymes involved in absorption, binding to B_{12} blood transport or intracellular proteins and/or B_{12} metabolism. However, no polymorphisms are analyzed through commercially available clinical tests that justify the use of any particular form(s) of B_{12}.

The current review shows that claims, such as "supplemental OHCbl delivers fewer methylating metabolites than supplemental MeCbl" are not scientifically substantiated. Supplemental OHCbl may deliver more, less, or the same amount of cobalamin inside cells as other B_{12} forms, thus resulting in the production of higher, lower, or equal amounts of intracellular MeCbl, respectively. That production depends on an individual's metabolism and particular SNPs, but those measures are not currently reported in commercial tests.

Ingestion of CNCbl results in lower tissue retention of active vitamin B_{12} than the naturally occurring forms of B_{12}, which may be particularly problematic in individuals with SNPs on B_{12} metabolic pathways. Researchers also have expressed concerns of potential cyanide accumulation in human tissues after long-term supplementation and/or intake from foods fortified with CNCbl. Thus, the CNCbl form of B_{12} seems to be an inferior choice despite its lower cost.

Conclusions

Most multivitamins and B-complex formulas available on the market contain B_{12} in the form of MeCbl, because it is the least costly form of natural B_{12} at this time. No reason exists to use other forms of B_{12} for supporting foundational needs for B_{12}, because the majority of individuals are likely able to metabolize it properly.

Often, the clinical picture warrants B_{12} supplementation in addition to food and to foundational supplementation with complex B vitamins. For that purpose, relatively high doses of B_{12}, in the vicinity of 1 to 3 mg/day, can be used with 2 major goals: (1) to take advantage of absorption by diffusion, bypassing the need for intrinsic factor; supplementing with high doses of MeCbl may work well in many individuals, and it is the most cost-effective, naturally occurring form of supplemental B_{12}; and (2) to cause the upregulation of some of the genetically impaired enzymes involved in B_{12} metabolism as is the case with many vitamin cofactors, to support the binding to various B_{12} cell receptors in the gut or other cells, or to encourage the binding to B_{12} transport proteins in the gut or in the blood.

Based on the considerations discussed in the current article, it is possible that individuals with particular SNPs affecting B_{12} assimilation might raise their B_{12} status more efficiently with 1 or more particular forms of vitamin B_{12}. However, because those types of SNPs are not currently reported in commercial tests, individuals may require either a trial-and-error approach by supplementing with one particular form of B_{12} at a time, or they might simply use a supplement with a combination of all 3 naturally occurring forms of B_{12} that are commercially available for a better chance of achieving faster clinical results. That approach may or may not offset genetic polymorphisms involving B_{12} metabolism and related pathways. The injectable form of B_{12} hydroxocobalamin is a justifiable choice when high dose oral B_{12} is not successful. This administration route may overcome severe absorption impairments due to pathologies or SNPs.[6]

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