The Crucial Factors of Cobalamin (Vitamin B12) Deficiency in Elderly

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Abstract

Among various concerns of elderly's health, vitamin deficiency, especially vitamin B12 or cobalamin, has found to be a key factor that deteriorates the major parts of the body. Vitamin B12 is essential for nerves, blood, and skeletal system. The major sources of vitamin B12 are animal products. The cause of the deficiency is not only insufficient consumption as we found in vegetarians but also the low quality of ingestion, transportation, and function of vitamin B12 in the B12 deficiency individuals, including the elderly. However, the mechanism of vitamin B12 is complicated. The reason may be due to the insufficient study to understand all the facts of the substance. This article will overview the already-known information concerning vitamin B12 and the causes of its deficiency in individuals and the elderly. In addition, the opinions for future approaches for developing the key information of the vitamin B12 for the general application will also be proposed.

Keywords**:** *Vitamin B12, Cobalamin, Deficiency, Elderly*

Introduction

As health care systems around the world allow us to live longer, the elderly require more health care concerns. The major lists of physical deterioration in the elderly are the nervous system, blood, and skeletal muscles. Besides of internal factors of individuals, external factors such as environment and nutrition are also the key factors to sustain the elderly's health. Sufficient nutrition is not about the quantity but the quality of the meals. People cannot just balance the staple foods of carbohydrate, proteins, and fat but also minerals and vitamin. The association of vitamin B12 deficiency and physical deterioration especially in the elderly are reported wisely (Oliveira Martinho et al., 2015; Khodabandehloo et al., 2015; Wang et al., 2009). Although, vitamin B12 deficiency can be treated by consumption of the vitamin B12 containing foods or even the supplementary vitamin, however, the solution is much more complicated. Intake high quantity of vitamin B12 cannot be a passport to build up the vitamin B12 sufficiency in all of the vitamin B12 deficiency individuals. Malabsorption and inactive forms of the vitamin B12 are believed to be great problems for most people who develop vitamin B12 deficiency. There are reports of high vitamin B12 in individuals including the elderly who do have the symptoms of vitamin B12 deficiency (Bates et al., 2003). In fact, significant numbers of individuals, who have sufficient amounts of vitamin B12 in the body, have low activity of the vitamin (Lee et al., 2003). This makes it more complicated and requires a lot more studies to understand the function(s) of the vitamin B12 for the optimal management to public health, especially for the elderly.

Composition and structure of Vitamin B12 (Cobalamin)

Vitamin B12 is a generic name of cobalamin. It is an organometallic complex compound of cobalt atom which makes it an important water-soluble vitamin for human health. As shown in figure 1, the cobalt atom forms 4 coordination sites to an organic compound of four reduced pyrrole rings which are linked together to form a macrocyclic ring, so-called corrin. The fifth co-ordinate binding position of cobalt is occupied with 5,6 dimethylbenzimidazole moiety while the sixth position can be engaged by any anion ligands (R) to generate various analogs of cobalamin, for examples, –CN (cyanocobalamin), -OH (hydroxycobalamin), -NO2 (nitrosylcobalamin), -SO3 (sulfitocobalamin), -CH3(methylcobalamin), H_2O (aquacobalamin) and – 5'-deoxy-5'-adenosyl (adenosylcobalamin). Based on its molecular structure, cobalamin will be more preferable to use for illustration in this article. There are approximately 20 analogs of cobalamin in which most of them do not have biological activity in human (Jagerstad and Arkbage,

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2003). Methylcobalamin and adenosylcobalamin are the only analogs of cobalamin that have been reported as the natural active forms of the cobalamin in a human body (Rietsema, 2014). On the other hand, cyanocobalamin and hydroxycobalamin are considered as the partial active analogs of cobalamin. Cyanocobalamin is a stable form of cobalamin in supplement food. It converts to be the active forms of either methyl or adenosylcobalamin in the human body. As same as cyanocobalamin, hydroxocobalamin can also turn to be the active cobalamin in a human body but, naturally, considered as the inactive (Gruber, Puffer, & Kraeutler, 2011; Hardlei et al., 2010). Rietsema (2014) reported that the severe cobalamin deficiency, such as dementia and psychosis, responded to treatment with high dose oral methylcobalamin, but not to equally high dose oral hydroxocobalamin.

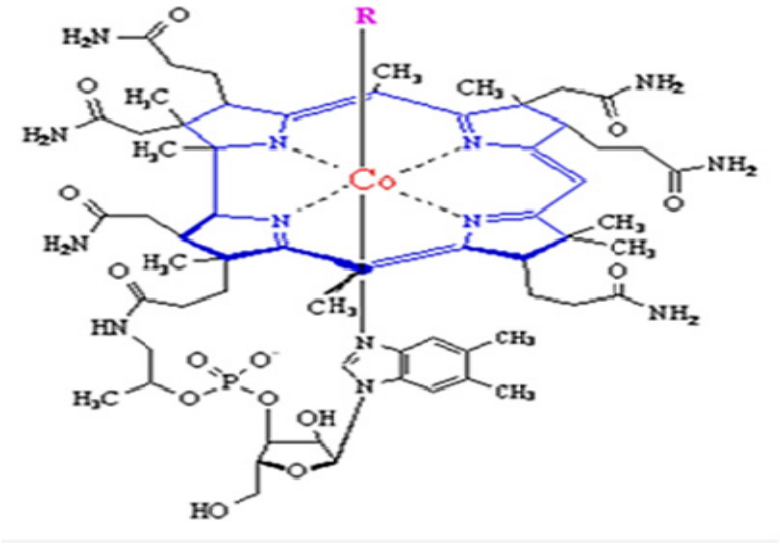

Figure 1 Chemical structure of vitamin B12, cobalamin, with cobalt constantly binds to 4 pyrrole rings of corrin and 5,6 dimethylbenzimidazole moiety. The last association of cobalt binding is R which represents an anion ligand which could be any molecules as mentions in the text and form different cobalamin analogs. **Source;** http://www.chm.bris.ac.uk/motm/vitaminb12/structure.html

The property and sources of vitamin B12 (Cobalamin)

Our body requires cobalamin for DNA synthesis and cellular metabolism. It is a water-soluble substance with a molecular weight of 1355.4 Da. (Watanabe, 2007). It is essential for the metabolism of the stable nutritional sources of carbohydrate, fat, and protein. Cobalamin is the crucial substance for red blood cell production and regeneration. Thus, the deficiency of cobalamin causes anemia as reported profoundly in the elderly (Dharmarajan et al., 2003; Andrès et al., 2004). Cobalamin is also the essential substance to synthesize myelin sheath of nerve fiber (Lövblad et al., 1997; Casella et al., 2005). In addition, the association between cobalamin and bone mineral density was also reported (Clarke et al., 2015; Ren et al., 2017).

Cobalamin can be produced naturally by the fermentation process of some microorganisms such as *Pseudomonas denitrificans* (Nguyen-Vo et al., 2018). Herbivorous ruminant, such as cattle and sheep, and fish require the cobalamin-producing bacteria from their environments and become their florae in the gastrointestinal tract to generate cobalamin (Watanabe & Bito, 2018). Thus, animal food products especially beef and fish, are the best sources of cobalamin for humans. Milk products and egg yolk are also alternative sources of cobalamin. Nevertheless, parenchymal organs such as the liver contain the richest

amount of cobalamin with over 100 µg/100 gram wet weight while the recommended consumption of cobalamin is approximately 2.4-2.8 µg daily. However, the requirements of cobalamin also vary by age and sex. Lactating women require higher and young children need less cobalamin.

Absorption of cobalamin

A human cannot synthesize cobalamin so we need to intake from the available foods of animal products. The major problem of cobalamin deficiency is the interruption of its absorption in some individuals. In general, cobalamin releases from the food by the role of gastric acid and pepsin in the upper gastrointestinal tract. In the cobalamin-containing foods, the cobalamin is cleaved from its binding protein by the role of hydrochloric acid in our stomach. People, especially the elderly, who have gastritis atrophy can lose the acid to cleave the binding protein and become cobalamin deficiency (van Asselt et al., 1996). After digested, all kinds of cobalamin analogs need haptocorrin (HC), which is an internal glycoprotein in gastric fluids, to carry on for further absorption process (Morkbak et al., 2007). In the duodenum, the HC molecule is degraded by the pancreatic protease enzymes. Hence, cobalamin binds to intrinsic factor (IF) to form the complex molecule of cobalamin-IF which then enters blood circulation at the distal ileum by the receptor-mediated process (Greibe et al., 2012). The circulating cobalamin then binds to a nonglycosylated protein, so-called transcobalamin (TC), as a carrier to enter the target cells by the process of endocytosis with their specific receptor molecules for metabolic propose (Guéant et al., 2001; Fyfe et al., 2004). There are three kinds of TC, I, II, and III. TC II represents about 10% of total transcobalamin and is the only cobalamin-transport protein that reaches target cell receptors (Fyfe et al., 2004). The TC II-cobalamin complex has a short half-life in blood circulation because of its rapid binding to the specific receptor to allow the cobalamin endocytosis into the target cells (Nielsen et al., 2012). Different tissues might use different receptor molecules to allow cobalamin endocytosis. In the liver, it is believed that cobalamin enters the cell via asialoglycoprotein (Ashwell et al, 1974; Burger et al., 1975). On the other hand, it enters the kidney via Lrp2/megalin (Moestrup et al., 1996). As reported by a different group of researchers, the absorption rates of cobalamin in different animal-food products might depend on the quantity and type of animal proteins. The cobalamin from eggs seems to have a lower rate of absorption than fish, chicken, and sheep (Doscherholmen et al., 1975; 1978; 1981; Watanabe, 2007). There was a report that the consumption of high dose oral supplemental cobalamin for at least 1 mg daily, about 1%–5% of free cobalamin can be absorbed via passive diffusion throughout the intestinal mucosa (Andrès et al., 2004). Approximately, there is 2-5 mg. of cobalamin storage in a body. The liver is the main storage of at least 1 mg while the kidney is the second main storage of cobalamin (Adams et al., 1972; Linnell et al., 1974). Cobalamin is sensitive to light exposer and can be converted to inactive by ascorbic acid. There is an obligatory loss of 0.1% per day (1.3 µg). Accordingly, it takes approximately 3 to 5 years to run out of cobalamin storages if dietary cobalamin is abruptly intaken for any reason. However, it is estimated that there is a turnover of 75% of cobalamin reabsorption secreted into bile by the enterohepatic circulation mechanism (Dharmarajan et al., 2003). Quantitatively, malabsorption is the main cause of cobalamin deficiency in human. However, the inactive forms of cobalamins are reported as the critical factor to cause cobalamin deficiency in elderly (Andrès et al., 2004; Wang et al., 2009; Khodabandehloo et al., 2015).

Activity of cobalamin

As mentioned, among various kinds of cobalamin analogs, only adenosylcobalamin and methylcobalamin are the active forms. The rest of the analogs are naturally inactive but some can be converted in a human body to be the active forms such as the cyanocobalamin. As shown in Figure 2 for the mechanism of cobalamin activity, adenosylcobalamin plays a role as an essential cofactor of mitochondrial methylmalonyl-CoA mutase to convert methylmalonyl-CoA to succinyl-CoA for the citric acid cycle (Takahashi-Iñiguez et al, 2012). Methylmalonyl-CoA is the thioester product of methylmalonic acid (MMA) and coenzyme A. The mal-functional activity of cobalamin causes the accumulation of MMA which its elevation might be used as an indicator for the low activity of cobalamin in a body (Selhub et al, 2009). On the other hand, the other active analog of methylcobalamin is a cofactor of cytosolic methionine

synthase to catalyse methylation of homocysteine to generate methionine which plays a role as a methyl donor for the synthesis of some crucial molecules such as myelin, serotonin and dopamine for the nervous system (Ikeda et al., 1998; Nishimoto et al., 2015). Besides the accumulation of MMA, homocysteine (Hcy) can also be used as the indicator of vitamin B12 deficiency (Carmel et al., 2003). However, there was a report that MMA might not be a good indicator for the patients over 70-year-old. The study reported that 20-25% of the elderly have the high level of MMA but approximately one-quarter of them do not have cobalamin deficiency (Bates et al., 2003; Dharmarajan et al., 2003; Manavifar, & Karimooy, 2013). Also, the mal-kidney function can accumulate MMA in the blood.

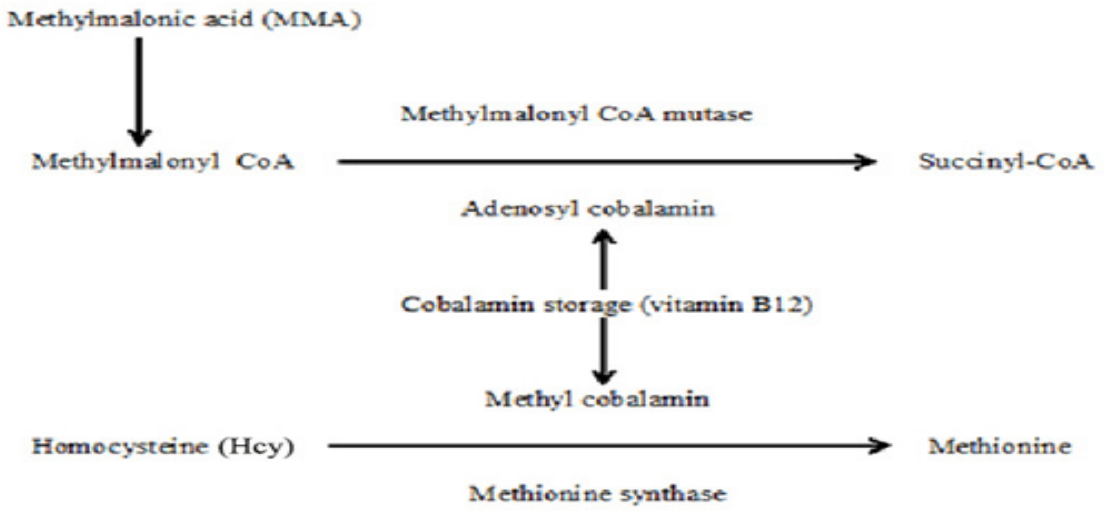

Figure 2 The two kinds of the active cobalamin (vitamin B12) analogs play the roles as the cofactors for the enzymatic reactions. The adenosyl-cobalamin co-ordinates to methylmalonyl CoA mutase to convert methylmalonyl-CoA,which is derived from methylmalonic acid (MMA), to succinyl-CoA. The other analog, methyl-cobalamin works with Methionine synthase to convert homocysteine to be methionine.

Future approaches

As of reports, there are four causes of cobalamin deficiency. Those involve consumption, ingestion, transportation and the activity of the cobalamin. Since cobalamin-rich foods are in animal products, vegetarians and poverty people prone to be the victims of the insufficient consumption of cobalamin (Allen et al., 2010). Elderly, who has the associated problem of health to digest meat such as toothless and gastritis atrophy is one of the most concerned population. Gastritis atrophy of parietal cells leads to hypochlorhydria. The insufficient amount of hydrochloric causes defection to elute cobalamin from the binding proteins. Although cyanocobalamin, which is an industrial-synthetic form of cobalamin, has been used wisely for supplementation, more information to study for its capacity in the long-term is required. It is important to educate people to know about the good sources of cobalamin with the comprehension that natural foods are the better sources of various vitamins especially cobalamin or vitamin B12. The study for the association of the cobalamin supplement and the cobalamin deficiency should be investigated more wisely in various populations especially in the elderly who are the great customers of the vitamin supplements products. The different forms of cobalamin gave different results to treat the patients who have cobalamin deficiency has been reported (Rietsema, 2014). Although cyanocobalamin has been

claimed to work sufficiently in the cobalamin deficiency individuals, there is no evidence to show that cyanocobalamin can be sustained and safe without any side effect (Moloney et al., 2008; Ullah et al., 2018). In the past, liver which is known as the richest source of cobalamin was effectively used to treat the suffering cobalamin deficiency patients. Unfortunately, the liver-extracted cobalamin, which is methyl and adenosyl-cobalamin, is heat labile and light sensitive (Juzeniene & Nizauskaite, 2013). This has been the reason to bring up cyanocobalamin as an alternative supplement to replace the liver-extracted cobalamin. Recently, there is a report that the cobalamin can keep being highly stable with the protein carriers (Wang et al., 2019). This means we should reconsider to use liver as the supplement source of vitamin B12 deficiency without any extraction process. The liver can simply process in the form of powder for the supplement of the cobalamin because liver-binding protein can naturally maintain the active forms of cobalamin. As a natural product of the liver powder with better technology of the pharmaceutical delivering system nowadays, the liver supplement should be the better choice for the cobalamin supplement to those individuals who are the high risk of the B12 deficiency. However, we should beware that the liver could accumulate some stable forms of toxic substances since one of the liver's major function is to neutralize toxic products in the host. Thus, some toxic substances might be accumulated. The farmed animals should be raised in this specific purpose to avoiding feeding with a high level of toxic substances. In addition, the shorter-lived animal might be the better object for preparation the liver powder to lessen the chance to expose the toxic substances.

There are reports of a high level of plasma cobalamin in the elderly who have the cobalamin deficiency and associated diseases with the high accumulation level of MMA and Hcy in their blood circulation. This can be interpreted that the elevated cobalamin level in those elderly is impaired to convert MMA and Hcy. This issue has not been truly proved. Thus, it will be interesting to identify and differentiate the active cobalamin, methylcobalamin, and adenosylcobalamin, out of the inactive analogs in these elderly. It should be possible to set up a laboratory test to identify the anion ligand (R) of the cobalamin in the old people who contain a high level of cobalamin. It will be great to understand more of the mechanism of the cobalamin analogs (Salnikov et al., 2014), especially all of the inactive forms of cobalamin. We should try to find the answer to explain for the reason of our body to store those inactive cobalamins if they do not give us an advantage. Although the inactive analogs cannot play the role of the cofactor to convert MMA and Hcy, they might have other function(s) in our body. Further study should process to answer this query. On the other hand, the other possible explanation of the elevated cobalamin, MMA and Hcy in the elderly could be due to the low-or-lack expression of cobalamin receptor gene(s) in the target cells. This can be a reason to explain why some of the elderly's blood contains a high level of cobalamin but cannot play its role. Cobalamin needs to enter the target cell because blood circulation does not seem to be a suitable environment for the action of the cobalamin. Thus, MMA and Hcy keep being elevated in the elderly population. Nevertheless, each cobalamin might have different mechanism and homeostasis in different environment and host. Thus, great amounts of study concerning the cobalamin derivatives are truly required.

In addition, it is well accepted that people who have pernicious anemia lack an intrinsic factor (IF) to carry cobalamin for absorption in the distal ileum. Additionally, the hereditary of the cobalamin's carrier deficiency such as hereditary IF deficiency which is caused by the recessive mutation of the IF expression gene has been reported (Tanner et al., 2005). Besides, there are also other carriers that play the role to carry cobalamins such as haptocorrin (HC) and Transcobalamin (TC). Haptocorrin plays a role in the gastrointestinal tract in the earlier stage before the intrinsic factor. Transcobalamin (TC) is another important factor to carry cobalamin in blood circulation to reach the target cell. It will be intriguing to understand the association of HC and TC for the cobalamin deficiency, this concern should pay more attention since it could be the alternative cause of the B12 deficiency in some individuals.

In conclusion, we still need a lot more information to learn about the cobalamin and the causes of its deficiency. We should understand the mechanism of all kinds of the cobalamin analogs, especially those inactive forms of cobalamin. If we do, we might be able to use them for some benefits for our body. We also require certainty that all the information that we have about cobalamin is absolutely correct. Since

cobalamin is a very important substance in our body, the complete and right information of the cobalamin can help us to live not only longer but also better.

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