# RELATIONSHIP BETWEEN B-VITAMINS AND BONE HEALTH

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***Abstract*: Nutrition is one of the most important modifiable factors involved in the development and maintenance of good bone health. Osteoporosis, a metabolic skeletal disease characterised by decreased bone mass and increased fracture risk, is a growing public health problem. B vitamins are a class of water-soluble vitamins that play important roles in cell metabolism. Though these vitamins share similar names, research shows that they are chemically distinct vitamins that often coexist in the same foods. In general, dietary supplements containing all eight are referred to as a vitamin B complex. Among the various risk factors for osteoporosis, calcium and vitamin D have well-established protective roles. Dietary modification is one effective approach for prevention of osteoporosis in the general population. The evidence, however, is not entirely consistent and as yet no clear mechanism has been defined to explain the potential link between B-vitamins and bone health. This review shows the emerging evidence of the supporting role of certain B Vitamins as modifiable factors associated with bone health.**

***Keywords*: Vitamin B, Osteoporosis, Bone health.**

## INTRODUCTION:

Vitamins are essential for normal physiological functioning of the body and are a group of organic compounds which are not synthesised endogenously by the body and henceforth have to be taken in small quantities from the diet. Vitamin deficiency accelerates the bones loss and leads to demineralization in bones which can be a major cause for hip fractures among elderly. Osteoporosis is a disease that affects many millions of people around the world. Then osteoporosis has no signs or symptoms until a fracture occurs – this is why it is often called a 'silent disease'. The WHO definition of osteoporosis is a bone mineral content (BMC) or bone mineral density (BMD), measured by techniques such as dual-energy X-ray absorptiometry, that is more than 22.5 SD below the young adult mean for the population[1]. The enhancement in bone fragility and continuous increase in fracture risk is characterised by destruction of the micro structure of bone tissue and by low bone mass [2]. Several reviewers have reported that other nutrients may also play important physiological roles in promoting bone health although calcium and vitamin D have been studied widely as essential factors for healthy bone [3]. Bone is a dynamic tissue which is in a constant state of remodelling where bone formation usually outweighs bone resorption, after a period of three decades bone resorption is favoured and bone loss ensues, which in turn predisposes older individuals to weaker bones and increased risk of fracture [4]. Osteoporosis as a result is not painful but the bones which are broken can cause significant pain, disability and even mortality. The most common sites for osteoporotic fractures are the, hip, spine and wrist with both spine and hip fractures are accompanied by considerable disability and increased morbidity and mortality.

The B vitamins are a group of nutrients that have been investigated for their possible roles in fracture risk and bone health. B vitamins generally serve as cofactors for the enzymes that are involved in the energy-producing metabolic pathways for fats, carbohydrates and proteins. B vitamins also play an important role in maintaining functions of the nervous system and B vitamins (including folate, B6, and B12) supplementation can effectively and easily modify high plasma homocysteine (Hcy). Each specific vitamin B (B1, B2, B3, B6, folate, and B12) has other roles in bone physiology as well. There are many articles related on B vitamins and bone health which mainly highlights on B9 (folate) and B12 (cobalamin) and B9 (folate), which help in the re-methylation of homocysteine metabolism and they are its cofactors [5] [6] [7]. This review gives information on the relationship between the B- vitamins and bone health and the vitamins in influencing bone quality, bone structure, bone mass and fracture risks from other reviewed and published articles.

**NUTRITION AND B VITAMINS:**

The B-vitamins comprise a group of eight water soluble vitamins that perform essential, closely inter-related roles in cellular functioning, acting as co-enzymes in a vast array of catabolic and anabolic enzymatic reactions. Their collective effects are particularly prevalent to numerous aspects of brain function, including energy production, DNA/RNA synthesis/repair, genomic and non-genomic methylation, and the synthesis of numerous neurochemicals and signalling molecules. The B Vitamins are thiamine (B1), riboflavin (B2), niacin (B3, also called nicotinamide or nicotinic acid amide), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid or folate (B9) and cobalamin (B12). In terms of their origins, the B vitamins are typically synthesised by plants, with their synthesis in plant chloroplasts, mitochondria and the cytosol carefully regulated to the plant's fluctuating requirements. In the plant they perform the same cellular functions as the roles that they will go on to play in the animals that consume them Though these vitamins share similar names, research shows that they are chemically distinct vitamins that often coexist in the same foods. A healthy diet can provide all the B Vitamin necessary to keep the body healthy, easily reaching the recommended dietary intakes. However, many people have an unbalanced diet, low in healthy foods (fruits, vegetables, meat, fish, cheese, eggs, legumes and cereals), and meaning that they do not get the recommended amounts. Especially in older persons, those with the highest fracture risk, intake is often a problem, and more importantly, the absorption of Vitamin B12 is reduced, leading to Vitamin B12 deficiencies in the elderly. In general, vitamin B complex is referred to as dietary supplements containing all eight B vitamins. Although most vitamins are derived ultimately from plants, they are often consumed indirectly from higher up the food chain in foods of animal origin, including meat, dairy and eggs; sometimes in forms that have already undergone some form of initial tailoring for bioactivity B vitamins are found in whole unprocessed foods. Processed carbohydrates such as sugar and white flour which tend to have lower B vitamin than their unprocessed parts. Turkey, liver and tuna have high concentrations of B vitamins [8]. Supplements containing B vitamin are generally thought to be safe, but should not be consumed in very large doses. Possible side effects can vary, depending on which B vitamin is taken [9]. Good sources for B vitamins include legumes (pulses or beans), chili peppers, tempeh, nutritional yeast, brewer's yeast, molasses, whole grain and potato. Another popular means of increasing one's vitamin B intake is by the consumption of dietary supplements. B vitamins are also commonly added to energy drinks, many of which have been marketed with large amounts of B vitamins [10]. In case of severe deficiency B vitamins and of vitamin B12, it may also be delivered by injection to reverse deficiencies.

**VITAMIN B1 (THIAMIN):**

Vitamin B1, or thiamin, in the active form, thiamin pyrophosphate (TPP), is an important cofactor for the key enzymes involved in the metabolism of carbohydrates, lipids and amino acids [11]. A coenzyme in the catabolism of sugars and amino acids. Whole-grain foods, wheat germ and yeast extract, and pork meat products are good food sources of vitamin B1. Like other B-complex vitamins, thiamine improves the body's ability to withstand stressful conditions and fight against the foreign bodies. It is named B1 because it was the first B vitamin discovered. The evidence of vitamin B1 and bone health is scarce. In Singapore Chinese Health Study, dietary intake of thiamine reduced the risk of hip fracture in either men or women [12]. A recent study has reported that thiamin status was deficient among patients with femoral neck fracture but not among those who were admitted for total hip replacement [13]. Due to mitochondrial dysfunction in focal regions of the brain, thiamin deficiency can impair energy metabolism [14], this in turn can increase the risk of Alzheimer's disease and cardiac failure, and therefore can increase the propensity to fall in the elderly. Vitamin B1 (thiamine) can be found in multivitamins (including children's chewable and liquid drops), B complex vitamins, or it can be sold individually. It is available in a variety of forms, including tablets, soft gels, and lozenges. It may also be labelled as thiamine hydrochloride or thiamine mononitrate. Thiamine can be administered intravenously also in case of severe deficiency.

**VITAMIN B2 (RIBOFLAVIN):**

It is a precursor of cofactors called FAD and FMN, which are needed for flavoprotein enzyme reactions, including activation of other vitamins. They participate in the oxidation-reduction reactions in the metabolic pathways that are involved in energy production. In addition to producing energy for the body, riboflavin works as an antioxidant, fighting damaging particles in the body known as free radicals. Free radicals can damage cells and DNA, and may contribute to the aging process, as well as the development of a number of health conditions, such as heart disease and cancer. Cereals, meat, fatty fish, and dark-green vegetables and good dietary sources of riboflavin. Also, milk and dairy products fortified with B2 are the biggest dietary contributors in Western countries [15]. The evidence of vitamin B2 and bone health is scarce, although few observational studies have been carried out to determine the relationship between vitamin B2 and bone health. The proposed mechanism on riboflavin and bone health is related to the coenzymatic form flavin adenine dinucleotide (FAD), which is a cofactor for the *MTHFR* enzyme. Studies suggest that the reduced activity of the thermolabile *MTHFR* enzyme seen in the *TT* genotype is due to the inappropriate loss of its B2 cofactor, this in turn have reduced activity of the *MTHFR* enzyme only in the presence of insufficient B2 status in individuals with the *TT* genotype [16]. In the Rotterdam study, the highest risk of fracture was also reported among women who were in both the lowest quartile intake of B2 and the *TT* genotype [17].

**VITAMIN B3 (NIACIN):**

Niacin is an organic compound known as vitamin B3 with 20 to 80 requisite human nutrients. The biosynthesis of B3 in humans is through the tryptophan-niacin conversion, where the production depends on other nutritional and hormonal factors, such as vitamin B6, B2, and iron, all of which serve as cofactors for the enzymes in the conversion pathway. Niacin is found in variety of foods, including liver, chicken, beef, fish, cereal, peanuts, and legumes, and is also synthesized from tryptophan, an essential amino acid found in most forms of protein. There are two co-enzyme forms of niacin: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Both play an important role in energy transfer reactions in the metabolism

of glucose, fat and alcohol [18]. A case-control study among postmenopausal Korean women showed that the lowest risk of osteoporosis was found in women in quartile two versus the lowest quartile intake of niacin, but there was no significant difference in risk among women in the two upper quartiles [19]. In the Singapore Chinese Health Study, no apparent association was found between B3 intake and risk of hip fracture. Another study among Japanese women showed a positive significant relationship between dietary intake of B3 and BMD in premenopausal women [20]. Although further investigations are needed to study about the fracture risks in elders with supplementation of niacin.

**VITAMIN B6 (PYRIDOXINE):**

Vitamin B6 is part of the vitamin B group, and its active form, pyridoxal 5'-phosphate (PLP) serves as a coenzyme in many enzyme reactions in amino acid, glucose, and lipid metabolism. Vitamin B6 in its metabolically active form is involved in many aspects of macronutrient metabolism, neurotransmitter synthesis, haemoglobin synthesis, histamine synthesis and gene expression. The liver is the site for vitamin B6 production. Vitamin B6 cannot be synthesized in the body and is therefore obtained from the diet. Vitamin B6 is found in a variety of foods, including fish, poultry, nuts, legumes, bananas and potatoes. Doses of Vitamin B6 above 200 mg were associated with cancer and neurotoxicity [21].

The role of vitamin B6 in fracture risk has shown to be independent of BMD and homocysteine, as further adjustment for these two variables did not affect the risk estimates substantially [22]. An enzyme required for collagen cross-linking; known as lysyl oxidase for which vitamin B6 acts as an essential coenzyme suggesting that low vitamin B6 may be detrimental for collagen cross-linking and result in poorer bone mechanical performance [23]. Through the modulation of the transcriptional activation in order to regulate the physiological actions of the hormone receptors vitamin B6 acts as a regulator of the steroid hormones including estrogen [24]. In another study, which examined older men and women, it has been shown that subjects who showed low plasma concentrations of Vitamin B6 (<20 nmol L−1) had been associated with a difference in the bone morphology [25].

In the Singapore Chinese Health Study, there found to be a dose-dependent inverse association between hip fracture risk and dietary intake of B6 among women but not among men. Furthermore, this association was present among women without a history of diabetes, but was attenuated and non-significant among women with diabetes. The influence of B6 in risk of hip fracture may get modifies by gender and diabetes [26]. The hypothesis produced from the above studies should undergo further clinical trials and needs to be validated in further studies.

**VITAMIN B12 (COBALAMIN):**

Vitamin B12, also called cobalamin, is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system, and the formation of red blood cells. It is one of eight B vitamins. It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid and amino acid metabolism [27]. Vitamin B12 exists in several forms and contains the mineral cobalt, so compounds with vitamin B12 activity are collectively called "cobalamins". Methylcobalamin and 5-deoxyadenosylcobalamin are the forms of vitamin B12 that are active in human metabolism.The enzyme is also involved in the cellular metabolism of carbohydrates, proteins and lipids. The vitamin B12 is only derived from animal sources which includes shellfish, meat, eggs and milk products. B12 was the first revealed to be related to osteoporosis and fractures in patients with pernicious anaemia [28]. Findings from a small clinical trial showed significantly a subsequent rise in alkaline phosphatase level following B12 supplementation in the deficient patients and lower alkaline phosphatase (a marker of bone formation) in vitamin B12 deficient patients, such findings suggest a protective effect of vitamin B12 on bone formation [29]. Clemens et al. observed that mice deficient in the synthesis of Vitamin B12 have a comparative scarcity of osteoblasts and growth retardation. Evidence emerging in vivo suggests that Vitamin B12 may interfere with growth hormone signalling in these mice and exert its downstream effects on osteoblasts [30]. A randomized controlled trial had been conducted which tried to determine whether Vitamin B12 and folic acid supplementation reduces osteoporotic fracture incidence in hyper homocysteinemic elderly individuals [31]. Data from this study show that combined Vitamin B12 and folic acid supplementation had no effect on osteoporotic fracture incidence in an elderly population. Moreover, trials involving supplementation of folate, vitamins B12 and B6, and thereby lowering homocysteine concentrations, which have failed to bring a turnover in bone health; suggesting that if a benefit of B-vitamin supplementation, or homocysteine lowering, on bone health exists, it is independent of any effect on bone turnover [32]. Vitamin B12, in the form of cyanocobalamin and occasionally hydroxocobalamin, can be administered parenterally as a prescription medication, usually by intramuscular injection [33]. Parenteral administration is typically used to treat vitamin B12 deficiency caused by pernicious anemia and other conditions that result in vitamin B12 malabsorption and severe vitamin B12 deficiency. Although Vitamin B12 deficiency is known to damage the myelin sheath covering cranial, spinal and peripheral nerves, the biochemical processes leading to neurological damage in Vitamin B12 deficiency are not yet fully understood. It is apparent that the interrelationship between the B-vitamins and bone health is complicated, and probably multi-factorial, which need to undergo further trials to elucidate the maximum potential of the mechanisms.

**GENETIC STUDIES:**

Several epidemiological studies have been performed investigating the relationship between MTHFR 677C_T polymorphism in the gene that encodes for the MTHFR enzyme and fracture risk and bone health [34]. Methylene reductase catalyzes the conversion of 5,10-methylene-5-methylene, and is used for the methylation of homocysteine to methionine, thereby reducing the concentration of homocysteine [8]. The Aberdeen Osteoporosis Screening Study showed that a low intake of riboflavin (vitamin B2) in subjects with the TT genotype had a negative effect on the BMD of the femoral neck [35]. The 677C_T polymorphism in the MTHFR gene is commonly reported as the most commonly occuring genetic determinant of hyperhomocysteinemia (>15 μmol L−1). The variant enzyme develops a greater intensity to disrupt from the FAD. Riboflavin in the form of FAD acts as a cofactor for MTHFR. The

677C_T polymorphism was linked with BMD at all measured sites, with an increase of 23% in the risk factor for all fractures in individuals with the MTHFR 677TT genotype compared with those with the CT or CC genotypes [36]. The Aberdeen Osteoporosis Screening Study showed that a reduced intake of riboflavin (vitamin B2) in subjects with the TT genotype had a negative effect on the BMD of the femoral neck [35]. The Rotterdam study, regarding osteoporosis, BMD and the onset of vertebral fractures, showed that a rise in the levels of homocysteine is a strong factor of indication and independent risk for osteoporotic fractures [36]. A study related to this in which the clinicians had examined the association between intake of Hcy-related B Vitamin (riboflavin, pyridoxine, folate and Vitamin B12) and femoral neck bone mineral density (FN-BMD) and the risk of fracture in a large population of elderly Caucasians and concluded that increased dietary riboflavin and pyridoxine intake was associated with higher FN-BMD [37] [38. In the Mendelian studies conducted, it showed that homozygosity for the variant allele (TT genotype) for the ethnic groups occurs at a rate of 25%, this leads to a 25% increase in tHcy concentrations than which occurs in individuals with the common genotype (CC). Studies have reported that individuals with the TT genotype and low folate levels (<9 nmol L−1) had a lower BMD than those with CC or CT genotypes at the same concentration of plasma folate, thereby following and suggesting an important gene-nutrient interaction [39]. In affirmation to these findings, a Danish Osteoporosis Prevention Study has concluded that individuals with the TT genotype had a significantly reduced BMD with low dietary intakes associated with various B Vitamins, including folic acid, B12, B6 and riboflavin was concluded by a Danish Osteoporosis Prevention Study [40]. These findings provide data to support a detrimental effect of the polymorphism combined with low B vitamin intakes on robust bone health outcomes (i.e., BMD and fracture risk) and also show that B Vitamins may have the potential to change any negative effect of this polymorphism on bone health. Factors such as variations in age and difference in ethnicity (considerable variation in the frequency of this polymorphism between populations) of the populations investigated probably also contribute to inconsistencies among studies [41] [42] [43].

**CONCLUSION:**

There is continuous observational evidence of an association of B-vitamins with bone health. Current evidence from the experimental studies have shown various pathways for the effect of vitamin B6 and vitamin B12 on bone physiology. There are still conflicting data regarding the relationship between high levels of homocysteine, low concentrations of B Vitamins and low bone mineral density. This epidemiological evidence is further reinforced by genetic studies that show an association between the common MTHFR 677C_T nutrients 6 polymorphism and the risk of osteoporosis. Certainly, mechanisms related to changes in collagen cross-linking may lead to a change in bone structure. Future clinical studies should include dietary information which are enriched with B vitamins to examine their effects on bone mineral density, bone turnover and/or fracture risk in elderly individuals, and, thus, avoid the potential adverse effects from B vitamin supplementations. In all the clinical trial conducted the patients had normal levels of vitamin C and vitamin D. Additional studies are further required to show that the levels of Vitamin B are causally associated with the risk of osteoporosis and whether there are benefits given by the supplementation of Vitamin B for bone health.

**REFERENCES:**

1) Consensus Development Conference. Diagnosis, prophylaxis and treatment of osteoporosis. American Journal of Medicine 1991; 90: 107–10.
2) Tucker, K.L. Osteoporosis prevention and nutrition. Curr. Osteoporos. Rep. 2009, 7, 111–117.
3) Ahmadieh, H.; Arabi, A. Vitamins and bone health: Beyond calcium and vitamin D. Nutr. Rev. 2011, 69, 584–598.
4) McLean R.R., Hannan M.T. B vitamins, homocysteine, and bone disease: Epidemiology and pathophysiology. Curr. Osteoporos. Rep. 2007;5:112–119. doi: 10.1007/s11914-007-0026-9.
5) Herrmann M., Peter Schmidt J., Umanskaya N., Wagner A., Taban-Shomal O., Widmann T., Colaianni G., Wildemann B., Herrmann W. The role of hyperhomocysteinemia as well as folate, vitamin B(6) and B(12) deficiencies in osteoporosis: A systematic review. Clin. Chem. Lab. Med. 2007;45:1621–1632.
6) World Health Organization. Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis. WHO Technical Report Series 843. Geneva: World Health Organization, 1994.
7) Clayton P.T. B6-responsive disorders: A model of vitamin dependency. J. Inherit. Metab. Dis.2006;29:317–326. doi: 10.1007/s10545-005-0243-2.
8) Stipanuk, M.H. (2006). Biochemical, physiological, molecular aspects of human nutrition (2nd ed.). St Louis: Saunders Elsevier p.667
9) Food and Nutrition Board, Institute of Medicine . Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. National Academy Press; Washington, DC, USA: 1998. pp. 306–356.
10) Chris Woolston (July 14, 2008). "B vitamins don't boost energy drinks' power". Los Angeles Times. Archived from the original on 19 October 2008. Retrieved 2008-10-08.
11) Chisolm-Straker, M.; Cherkas, D. Altered and unstable: Wet beriberi, a clinical review. J. Emerg. Med. 2013, 45, 341–344.
12) Dai Z., Wang R., Ang L.W., Yuan J.M., Koh W.P. Dietary B vitamin intake and risk of hip fracture: The Singapore Chinese Health Study. Osteoporos. Int. 2013;24:2049–2059. doi: 10.1007/s00198-012-2233-1.
13) Older M.W., Dickerson J.W. Thiamine and the elderly orthopaedic patient. Age Ageing. 1982;11:101–107. doi: 10.1093/ageing/11.2.101.
14) Abdou E., Hazell A.S. Thiamine deficiency: An update of pathophysiologic mechanisms and future therapeutic considerations. Neurochem. Res. 2014;40:353–361. doi: 10.1007/s11064-014-1430-z.
15) Rivlin R.S. Riboflavin. In: Bowman B.A., Russell R.M., editors. Present Knowledge in Nutrition. ILSI Press; Washington, DC, USA: 2001. pp. 191–198.

16) McNulty H., McKinley M.C., Wilson B., McPartlin J., Strain J.J., Weir D.G., Scott J.M. Impaired functioning of thermolabile methylenetetrahydrofolate reductase is dependent on riboflavin status: Implications for riboflavin requirements. Am. J. Clin. Nutr. 2002;76:436–441.
17) Yazdanpanah N., Uitterlinden A.G., Zillikens M.C., Jhamai M., Rivadeneira F., Hofman A., de Jonge R., Lindemans J., Pols H.A., van Meurs J.B. Low dietary riboflavin but not folate predicts increased fracture risk in postmenopausal women homozygous for the MTHFR 677T allele. J. Bone Miner. Res. 2008;23:86–94. doi: 10.1359/jbmr.070812.
18) Whitney, N; Rolfes, S Crowe, T Cameron-Smith, D Walsh, A (2011). *Understanding Nutrition*. Melbourne: Cengage Learning.
19) Park, H.M.; Heo, J.; Park, Y. Calcium from plant sources is beneficial to lowering the risk of osteoporosis in postmenopausal korean women. Nutr. Res. 2011, 31, 27–32.
20) Sasaki, S.; Yanagibori, R. Association between current nutrient intakes and bone mineral density at calcaneus in pre- and postmenopausal japanese women. J. Nutr. Sci. Vitaminol. (Tokyo) 2001, 47, 289–294.
21) Schaumburg H., Kaplan J., Windebank A., Vick N., Rasmus S., Pleasure D., Brown M.J. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. N. Engl. J. Med. 1983;309:445–448. doi: 10.1056/NEJM198308253090801.
22) Yazdanpanah N., Zillikens M.C., Rivadeneira F., de Jong R., Lindemans J., Uitterlinden A.G., Pols H.A., van Meurs J.B. Effect of dietary B vitamins on bmd and risk of fracture in elderly men and women: The Rotterdam Study. Bone. 2007;41:987–994. doi: 10.1016/j.bone.2007.08.021.
23) Bird T & Levene C (1982) Lysyl oxidase – evidence that pyridoxal-phosphate is a cofactor. Biochem Biophys Res Commun 108, 1172–1180.
24) Allgood V.E., Cidlowski J.A. Vitamin B6 modulates transcriptional activation by multiple members of the steroid hormone receptor superfamily. J. Biol. Chem. 1992;267:3819–3824.
25) Holstein J.H., Herrmann M., Splett C., Herrmann W., Garcia P., Histing T. Low serum folate and vitamin B-6 are associated with an altered cancellous bone structure in humans. Am. J. Clin. Nutr. 2009;90:1440–1445. doi: 10.3945/ajcn.2009.28116.
26) Dai Z., Wang R., Ang L.W., Yuan J.M., Koh W.P. Dietary B vitamin intake and risk of hip fracture: The Singapore Chinese Health Study. Osteoporos. Int. 2013;24:2049–2059. doi: 10.1007/s00198-012-2233-1.
27) Yamada, Kazuhiro (2013). "Chapter 9. Cobalt: Its Role in Health and Disease". In Astrid Sigel, Helmut Sigel and Roland K. O. Sigel. Interrelations between Essential Metal Ions and Human Diseases. Metal Ions in Life Sciences 13. Springer. pp. 295–320.
28) Goerss J.B., Kim C.H., Atkinson E.J., Eastell R., O'Fallon W.M., Melton L.J., 3rd Risk of fractures in patients with pernicious anemia. J. Bone Miner. Res. 1992;7:573–579. doi: 10.1002/jbmr.5650070514.
29) Carmel R, Lau K, Baylink D et al. (1988) Cobalamin and osteoblast-specific proteins. N Engl J Med 319, 70–75.
30) Clemens T.L. Vitamin B12 deficiency and bone health. N. Engl. J. Med. 2014;371:963–964. doi: 10.1056/NEJMcibr1407247.
31) Van Wijngaarden J.P., Dhonukshe-Rutten R.A., van Schoor N.M., van der Velde N., Swart K.M., Enneman A.W., van Dijk S.C., Brouwer-Brolsma E.M., Zillikens M.C., van Meurs J.B., et al. Rationale and design of the B-PROOF study, a randomized controlled trial on the effect of supplemental intake of Vitamin B12 and folic acid on fracture incidence. BMC Geriatr. 2011;11
32) Green T, McMahon J, Skeaff C et al. (2007) Lowering homocysteine with B vitamins has no effect on biomarkers of bone turnover in older persons: a 2-y randomized controlled trial. Am J Clin Nutr 85, 460–464.
33) Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Loukili NH, Zimmer J, et al. B12 deficiency: a look beyond pernicious anemia. J Fam Pract 2007;56:537-42.
34) Carmel, R.; Green, R.; Rosenblatt, D.S.; Watkins, D. Update on cobalamin, folate, and homocysteine. Hematol. Am. Soc. Hematol. Educ. Program. 2003, 2003, 62–81.
35) Yamada, K.; Chen, Z.; Rozen, R. Effects of common polymorphisms on the properties of recombinant human methylenetetrahydrofolatereductase. Proc. Natl. Acad. Sci. USA 2001, 98, 14853–14858.
36) Wang, H.; Liu, C. Association of MTHFR C667T polymorphism with bone mineral density and fracture risk: An updated meta-analysis. Osteoporos. Int. 2012, 23, 2625–2634.
37) Macdonald, H.M.; McGuigan, F.E.; Fraser, W.D.; New, S.A.; Ralston, S.H.; Reid, D.M. Methylenetetrahydrofolatereductase polymorphism interacts with riboflavin intake to influence bone mineral density. Bone 2004, 35, 957–964.
38) Gjesdal C.G., Vollset S.E., Ueland P.M., Refsum H., Meyer H.E., Tell G.S. Plasma homocysteine, folate, and vitamin B 12 and the risk of hip fracture: The hordaland homocysteine study. J. Bone Miner. Res. 2007;22:747–756. doi: 10.1359/jbmr.070210.
38) Yazdanpanah, N.; Zillikens, M.C.; Rivadeneira, F.; de Jong, R.; Lindemans, J.; Uitterlinden, A.G.; Pols, H.A.; van Meurs, J.B. Effect of dietary B vitamins on BMD and risk of fracture in elderly men and women: The Rotterdam study. Bone 2007, 41, 987–994.
39) Abrahamsen, B.; Madsen, J.S.; Tofteng, C.L. Stilgren, L.; Bladbjerg, E.M.; Kristensen, S.R.; Brixen, K.; Mosekilde, L. Are effects of MTHFR (C677T) genotype on BMD confined to women with low folate and riboflavin intake? Analysis of food records from the Danish osteoporosis prevention study. Bone 2005, 36, 577–583.
40) Clarke, M.; Ward, M.; Strain, J.J.; Hoey, L.; Dickey, W.; McNulty, H. B-vitamins and bone in health and disease: The current evidence. Proc. Nutr. Soc. 2014, 73, 330–339.
41) Madigan S.M., Tracey F., McNulty H., Eaton-Evans J., Coulter J., McCartney H., Strain J.J. Riboflavin and vitamin B-6 intakes and status and biochemical response to riboflavin supplementation in free-living elderly people. Am. J. Clin. Nutr. 1998;68:389–395.
42) Powers H.J. Current knowledge concerning optimum nutritional status of riboflavin, niacin and pyridoxine. Proc. Nutr. Soc. 1999;58:435–440. doi: 10.1017/S0029665199000579.