ISSN No:-2456-2165

Ramifications of Vitamin B12 Deficiency and its Beneficial Effects

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Abstract: - Vitamin B12 (methylcobalamin) deficiency can lead to a variety of health problems, including anaemia, fatigue, weakness, and memory loss. If left untreated, it can also lead to more serious problems such as nerve damage and problems with vision, hearing, and balance. Methylcobalamin, an active form of vitamin B12, aids in producing S-adenosylmethionine and methionine. It is necessary for the synthesis of DNA, the appropriate creation of red blood cells, the integrity of myelin, and brain function. Worldwide, the most common form of vitamin B12 insufficiency is observed among vegetarians, and its equivalent, methylcobalamin, may help. The majority of common illnesses, including cardiovascular disorders, diabetes, anaemia, Hyperhomocysteinemia, and degenerative conditions, may benefit from this medication. Methylcobalamin enhances correct neuron function, which lessens the symptoms of Alzheimer's disease, Parkinsonism, dementia, and neuropathic syndromes. It also aids in the production of neuronal lipids and the regeneration of axonal nerves. Peripheral neuropathy may be treated with it. Also, taking methylcobalamin supplements has been shown to ease the symptoms of Parkinson's disease, speed up remyelination in diseases that damage the nerves (which is why this compound is used in experiments), and help the body make more red blood cells.

***Keyboard*:-** *Methylcobalamin, Neuropathy, Methionine, Deficiency, Homocysteine.*

I. INTRODUCTION

Methylcobalamin is a strong and functional version of the nutrient cyanocobalamin. It is essential for maintaining one's health. A lack of dietary cobalamin may result in a variety of grave health issues[1]. Insufficiency of blood, sadness, irritability, and psychosis are the most prevalent. A chronic lack of vitamin B_{12} may cause Hyperhomocysteinemia and ultimately a cardiovascular problem[2]. In the modern world, healthcare is crucial to our daily lives. This combines a significant obligation to better and save thousands of lives worldwide. Even though health has advanced dramatically since 1950, a lot of problems still need to be addressed[3]. Noncommunicable illnesses such as cancer, chronic lung disease, anaemia, diabetes, Hyperhomocysteinemia, and over 17.5 million fatalities from cardiovascular disease in 2005 account for 36 million deaths annually[4]. If this is not a serious and sensitive enough issue, obesity is also a major concern in some parts of the world, with a quarter of the world's population being overweight and another quarter undernourished[5]. And if this is not enough, we should consider the massive number of people living on less than $1 a day and the number of individuals who die prematurely due to health-related factors such as poverty, malnutrition, and preventable illnesses[6]. For example, the economic costs imposed by illness are estimated at over $4.6 trillion per year in high-income nations alone. Obviously, medicine and its applications play a key role in life and our existence on this planet[7]. However, these numbers could even be considered insignificant when we take into consideration the number of people who die every year as a consequence of preventable diseases that could be eliminated with improved nutrition and public health interventions[8].

The absence of important nutrients like folate and vitamin B_{12}, which humans cannot produce, is thought to be a global health issue since it may lead to anaemia and brain malfunction[9]. Those who are elderly or pregnant are more likely to have a vitamin B_{12} deficiency. Methylcobalamin, often known as mecobalamin or methyl B_{12}, is an analogue of vitamin B_{12} that may be used to treat or prevent pathologies brought on by vitamin B_{12} deficiency[10]. It differs from cyanocobalamin because it includes cyanide and has methyl alkyl linkages. It is created in a lab by reducing cyanocobalamin with sodium borohydride in an alkaline solution, followed by the addition of methyl iodide[11]. It possesses an octahedral cobalt (III) core. In the central nervous system, methylcobalamin (5 mg, 60 mg vegetarian lozenges) is active[12].

II. DEFICIENCY OF VITAMIN B12

Cobalamin, often known as vitamin B_{12}, is a water-soluble vitamin that is found in foods including dairy, eggs, and red meat. A glycoprotein called intrinsic factor, which is produced by parietal cells in the stomach, is required for B_{12} absorption in the terminal ileum[13]. After being absorbed, B_{12} is employed as a cofactor for enzymes that are involved in the production of DNA, fatty acids, and myelin. Hematologic and neurologic problems might therefore result from B12 insufficiency[14]. B_{12} is stored in excess in the liver, but when it cannot be absorbed for an extended length of time (due to nutritional insufficiency, malabsorption, or a lack of intrinsic factor, for example), hepatic reserves are depleted, and a shortage results[15]. The deficiency manifests initially as megaloblastic anaemia, in which red blood cells are larger than normal because they are immature. B12 is involved in the formation of DNA, fatty acids, and myelin[16]. The neurologic manifestations of B_{12} deficiency include paraesthesia (sensations of tingling and numbness in the hands and feet), tremors, progressive weakness, and reflex changes[17].

III. PATHOPHYSIOLOGY

A protein known as R-factor, which dietary vitamin B_{12} interacts with, is secreted by the salivary glands in healthy people[18]. Once the mixture enters the small intestine, pancreatic enzymes remove the B_{12} from the R-factor so that it may connect to an intrinsic factor, a glycoprotein produced by the gastric parietal cells[19]. The newly created compound of vitamin B12 and intrinsic factor may then attach to receptors on the ileum, allowing for B_{12} absorption[20]. After ingestion, B_{12} takes part in metabolic activities that are essential for hematologic and neurologic functions. No matter the reason, if B_{12} cannot be absorbed, a number of deficiencies may manifest[21].

The enzyme methionine synthase, which is utilized to convert homocysteine into methionine, requires vitamin B_{12} as a cofactor. By products of this reaction include the conversion of methyl-THF to THF and intermediates required for the production of the pyrimidine nucleotides found in DNA[22]. Homocysteine cannot be converted to methionine with B_{12} insufficiency, and as a result, methyl-THF cannot be converted to THF. Homocysteine levels rise as a consequence, and the inability to synthesize pyrimidine bases slows down DNA synthesis, resulting in megaloblastic anaemia[23]. Symptoms of weariness and pallor, which are often seen in people with B12 deficiency, are then brought on by the anaemia. Polymorphonuclear leukocytes and other rapidly proliferating cell lines are negatively affected by decreased DNA synthesis (PMNs)[24]. Consequently, B_{12} insufficiency often causes a condition known as pernicious anaemia, which causes symptoms of hypersensitivity to touch and sound, psychosis, peripheral neuropathy (tingling or numbness in the hands and feet), tinnitus (ringing in the ears), megaloblastic anaemia[25].

The enzyme methylmalonyl-CoA mutase, which changes methylmalonyl-CoA into succinyl-CoA, also uses vitamin B_{12} as a cofactor. Methylmalonic acid (MMA) levels will rise in people with a B_{12} deficiency because it cannot be converted to succinyl-CoA[26]. The neurologic impairments, such as neuropathy and ataxia, reported in these individuals are thought to be caused by myelin degradation, which is thought to be exacerbated by increased levels of MMA and homocysteine[27]. Subacute combined degeneration of the spinal cord is a disorder brought on by myelin degradation (SCDSC). The dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts are among the areas of the spinal cord affected by this illness, which also causes dementia, ataxia, peripheral neuropathy, and loss of proprioception[28].

IV. BENEFICIAL USE OF METHYLCOBALAMIN

Methylcobalamin's urine excretion in humans is around one-third that of cyanocobalamin at the same dosage, which suggests increased tissue retention. When taken for 16 weeks at a dosage of 6 mg per day, it increases sperm count by 37.5%[29]. Sperm concentration rises by 38% when administered at a dosage of 1,500 micrograms per day for four to twenty-eight weeks, and sperm motility improves in 50% of instances[30]. Chronic exposure to methylcobalamin and SAMe protected against glutamate neurotoxicity. Chronic SAMe administration also prevents sodium nitroprusside-induced neurotoxicity, which is mediated by nitrous oxide[31]. Additionally, a continuous dosage of it stimulates protein synthesis by up-regulating gene transcription. Through the methylation cycle, methylcobalamin improves neuronal survival and neurite development and raises ERK 12 and AKT activity at concentrations of over 100 nm[32]. SAMe increases the levels of neurotransmitters, phospholipids, biogenic amines and their metabolites. Because SAMe has so many uses, it is being looked at as a treatment for a wide range of health problems, such as depression, schizophrenia, and stroke[33].

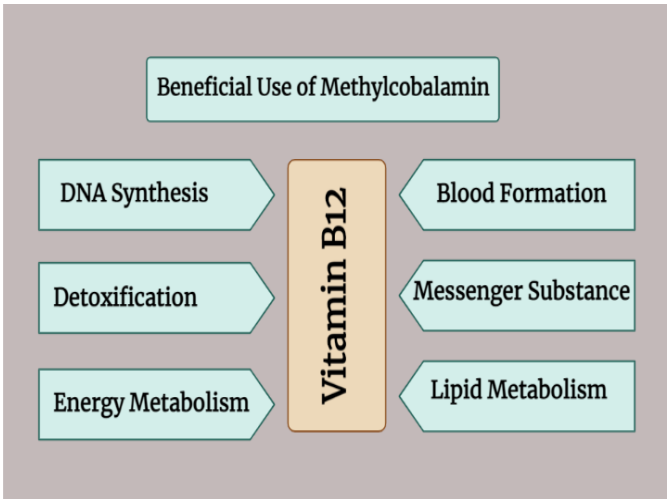

Fig 1 Beneficial Use of Methylcobalamin

V. MECHANISMS OF ACTION

It functions in the synthesis of myelin, a substance that coats and protects nerve fibers. The injured neuron is rejuvenated by methylcobalamin. Lack of methylcobalamin causes improper myelin sheath formation, which damages nerve fibers and causes irreparable nerve damage[34]. For optimal absorption, an intestinal tract intrinsic factor created in the stomach must exist. People who lack this component exhibit vitamin B12 deficits, such as pernicious anaemia (a gradual, sneaky condition that may be fatal)[35]. In reality, pernicious anaemia implies "leading to death." The methionine transferase enzyme, which uses the folate cycle to change the amino acid homocysteine into methionine, uses methylcobalamin as a cofactor. When two metabolites are altered, the amino acid is converted into the metabolite homocysteine, a precursor to creatine synthesis[36]. This uses the folate cycle to change homocysteine into methionine, a precursor to creatine synthesis. When methylcobalamin is present, the enzyme might change the homocysteine into methionine (the reason why we should supply our bodies with an adequate level of B12), which is one of the starting points for creatine synthesis[37]. It is made out of the amino acid methionine, which is an essential metabolite in the urea cycle to determine whether the methionine-transferase enzyme requires vitamin B12 to convert homocysteine into methionine, or if the change can be made another way. The folate cycle is necessary because it allows the body to convert homocysteine into methionine, which is one of the starting points for creatine synthesis[38].

VI. PHARMACOKINETICS AND DOSAGE

Methylcobalamin may be given parenterally, intravenously, or orally. Methylcobalamin forms a compound with an intrinsic factor absorbed in the distal ileum. It has a six-day half-life. A highly specialized receptor-mediated transport mechanism mediates the absorption[39]. When it binds to Transcobalamin II, a B-globulin carrier protein, it is disseminated to all of the body's cells. It is then stored in the liver for 300–500 micrograms. Bile is used to expel it. The bioavailability of methylcobalamin in nasal spray is 9%[40]. Methylcobalamin should be taken daily at a level of 500 mcg to relieve stress. A daily dosage of 1500 mcg may be given safely in situations of acute neuropathy. For age-related brain deterioration, a dose of 1 mg daily is necessary[41]. Methylcobalamin may be taken with a comparable amount of pyridoxine and folic acid. A daily intake of 100 mg may balance the intestinal demand for vitamin B12, which is only a problem for severe vegetarians[42]. Every human being needs at least 3 mg of this medication each day to provide basic nerve support. To keep the medication dry, it is kept in the refrigerator at or below 41°F (5°C). Additionally, methylcobalamin is administered deeply into the muscles[43].

VII. TRANSPORT MECHANISMS FOR VITAMIN B12 IN INDIVIDUALS

The metabolism benefits from vitamin B_{12}. Energy is made and used by the body's metabolic functions, which include digestion, absorption, excretion, breathing, circulation, and controlling body temperature. The digestive system of humans has a sophisticated system for absorbing dietary vitamin B_{12}[44]. In the stomach, haptocorrin, a protein that binds vitamin B12, initially releases vitamin B_{12} from dietary protein. The liberated vitamin B_{12} binds to intrinsic factor (IF, gastric vitamin B_{12}-binding protein) in the proximal ileum after the proteolysis of the haptocorrin-vitamin B_{12} complex by pancreatic proteases in the duodenum[45]. By means of receptor-mediated endocytosis, the IF-vitamin B_{12} combination may get into mucosal cells in the distal ileum. This gastrointestinal absorption has a considerable impact on the bioavailability of dietary vitamin B_{12}. Recent research suggests that vitamin B12 may lower the risk of a number of long-term illnesses and birth defects[46].

The way PA is handled differs from nation to nation and from region to region. Although there is no known permanent treatment for PA, it is anticipated that replenishing B_{12} will stop anaemia-related symptoms, stop the neurological decline, and, in cases where neurological issues are not advanced, restore neurological function and cause complete and long-lasting remission of all symptoms[47]. There are several methods for replenishing B_{12}. Natural healthcare professionals seem to be split on whether vitamin B_{12} therapy for individuals with pernicious anaemia should be administered orally, intramuscularly, via a buccal patch, or in any other way[48]. It's difficult to investigate supplements since the majority of scientific studies appear to be inconclusive and cannot determine whether treatment is effective. Despite having the best interest of their patients in mind, naturopathic physicians in Oregon will be forced to choose between offering treatment they believe is scientifically proven and can completely alleviate symptoms, or practicing medicine with their limited scope of practice as dictated by a regulatory organization, presumably using out-of-date reference materials[49].

VIII. CONCLUSION

Methylcobalamin is an active form of vitamin B_{12} and aids in producing S-adenosylmethionine and methionine. It also enhances correct neuron function, which lessens the symptoms of Alzheimer's disease, Parkinsonism, dementia, and neuropathic syndromes. Worldwide, the most common form of vitamin B_{12} insufficiency is observed among vegetarians. Methylcobalamin supports the body's ability to produce healthy blood cells and nerve cells. For those who cannot absorb vitamin B_{12} and/or suffer from its shortages, it is the finest therapy as well as a dietary supplement. Methylcobalamin monotherapy decreases neuropathic

symptoms as well as plasma/serum homocysteine levels. It seems that combination treatment with additional vitamin B complexes is more successful. So, it is possible to see methylcobalamin as one of the promising dietary supplements and medicines with a range of potential advantages.

REFERENCES

[1]. Wolffenbuttel BHR, Wouters HJCM, Heiner-Fokkema MR, Klauw MM van der. The Many Faces of Cobalamin (Vitamin B12) Deficiency. Mayo Clin Proc Innov Qual Outcomes 2019;3:200.
[2]. Sangle P, Sandhu O, Aftab Z, Anthony AT, Khan S. Vitamin B12 Supplementation: Preventing Onset and Improving Prognosis of Depression. Cureus 2020;12.
[3]. Braveman P, Gottlieb L. The Social Determinants of Health: It's Time to Consider the Causes of the Causes. Public Health Rep 2014;129:19.
[4]. Maron BA, Loscalzo J. The Treatment of Hyperhomocysteinemia. Annu Rev Med 2009;60:39.
[5]. Sahoo K, Sahoo B, Choudhury AK, Sofi NY, Kumar R, Bhadoria AS. Childhood obesity: causes and consequences. J Fam Med Prim Care 2015;4:187.
[6]. Saunders J, Smith T. Malnutrition: causes and consequences. Clin Med (Northfield Il) 2010;10:624.
[7]. Turner L. Life extension research: health, illness, and death. Health Care Anal 2004;12:117–29.
[8]. Kruk ME, Gage AD, Arsenault C, *et al.* High-quality health systems in the Sustainable Development Goals era: time for a revolution. Lancet Glob Heal 2018;6:e1196.
[9]. Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. Food Nutr Bull 2008;29:S126.
[10]. JK G, Sana QS. Potential Benefits of Methylcobalamin: A Review. Austin J Pharmacol Ther.
[11]. Gawande MB, Goswami A, Felpin FX, *et al.* Cu and Cu-Based Nanoparticles: Synthesis and Applications in Catalysis. Chem Rev 2016;116:3722–811.
[12]. Osman D, Cooke A, Young TR, Deery E, Robinson NJ, Warren MJ. The requirement for cobalt in vitamin B12: A paradigm for protein metalation. Biochim Biophys Acta Mol Cell Res 2021;1868.
[13]. Rizzo G, Laganà AS, Rapisarda AMC, *et al.* Vitamin B12 among Vegetarians: Status, Assessment and Supplementation. Nutr 2016, Vol 8, Page 767 2016;8:767.
[14]. Mahmood L. The metabolic processes of folic acid and Vitamin B12 deficiency. J Heal Res Rev 2014;1:5.
[15]. Ankar A, Bhimji SS. Vitamin B12 Deficiency. StatPearls August 2022.
[16]. Briani C, Torre CD, Citton V, *et al.* Cobalamin Deficiency: Clinical Picture and Radiological Findings. Nutrients 2013;5:4521.
[17]. Ekabe CJ, Kehbila J, Abanda MH, Kadia BM, Sama CB, Monekosso GL. Vitamin B12 deficiency neuropathy; a rare diagnosis in young adults: a case report. BMC Res Notes 2017;10.
[18]. Blakeley M, Sobczyńska-Malefora A, Carpenter G. The Origins of Salivary Vitamin A, Vitamin B12 and Vitamin D-Binding Proteins. Nutrients 2020;12:1–12.
[19]. Al-Awami HM, Raja A, Soos MP. Physiology, Gastric Intrinsic Factor. StatPearls July 2022.
[20]. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes 2021;12:916.
[21]. Dubaj C, Czyz K, Furmaga-Jabłońska W. Vitamin B12 deficiency as a cause of severe neurological symptoms in breast fed infant - A case report. Ital J Pediatr 2020;46.
[22]. Allen LH. Vitamin B-12. Adv Nutr 2012;3:54.
[23]. Hoffbrand A V., Jackson BFA. Correction of the DNA synthesis defect in vitamin B12 deficiency by tetrahydrofolate: evidence in favour of the methyl-folate trap hypothesis as the cause of megaloblastic anaemia in vitamin B12 deficiency. Br J Haematol 1993;83:643–7.
[24]. Socha DS, DeSouza SI, Flagg A, Sekeres M, Rogers HJ. Severe megaloblastic anemia: Vitamin deficiency and other causes. Cleve Clin J Med 2020;87:153–64.
[25]. Staff NP, Windebank AJ. Peripheral Neuropathy Due to Vitamin Deficiency, Toxins, and Medications. Contin Lifelong Learn Neurol 2014;20:1293.
[26]. Takahashi-Iñiguez T, García-Hernandez E, Arreguín-Espinosa R, Flores ME. Role of vitamin B12 on methylmalonyl-CoA mutase activity. J Zhejiang Univ Sci B 2012;13:423.
[27]. Azzini E, Raguzzini A, Polito A. A Brief Review on Vitamin B12 Deficiency Looking at Some Case Study Reports in Adults. Int J Mol Sci 2021;22.
[28]. Ota K, Yamaguchi R, Tsukahara A, *et al.* Subacute Combined Degeneration of the Spinal Cord Caused by Autoimmune Gastritis. Intern Med 2020;59:2113.
[29]. Beltrame FL, De Santi F, Vendramini V, *et al.* Vitamin B12 prevents cimetidine-induced androgenic failure and damage to sperm quality in rats. Front Endocrinol (Lausanne) 2019;10:309.
[30]. Kumar N, Singh A. Trends of male factor infertility, an important cause of infertility: A review of literature. J Hum Reprod Sci 2015;8:191.
[31]. Akinori Akaike, Yutaka Tamura, Yuko Sato, Takeharu Yokota. Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons. Eur J Pharmacol 1993;241:1–6.
[32]. Okada K, Tanaka H, Temporin K, *et al.* Methylcobalamin increases Erk1/2 and Akt activities through the methylation cycle and promotes nerve regeneration in a rat sciatic nerve injury model. Exp Neurol 2010;222:191–203.
[33]. Leppik L, Kriisa K, Koido K, *et al.* Profiling of amino acids and their derivatives biogenic amines before and after antipsychotic treatment in first-episode psychosis. Front Psychiatry 2018;9:155.

[34]. Wu F, Xu K, Liu L, *et al.* Vitamin B12 Enhances Nerve Repair and Improves Functional Recovery After Traumatic Brain Injury by Inhibiting ER Stress-Induced Neuron Injury. Front Pharmacol 2019;10.
[35]. Dholakia KR, Dharmarajan TS, Yadav D, Oiseth S, Norkus EP, Pitchumoni CS. Vitamin B12 deficiency and gastric histopathology in older patients. World J Gastroenterol 2005;11:7078.
[36]. Lodowski P, Jaworska M, Garabato BD, Kozlowski PM. Mechanism of Co-C Bond Photolysis in Methylcobalamin: Influence of Axial Base. J Phys Chem A 2015;119:3913–28.
[37]. Ducker GS, Rabinowitz JD. One-Carbon Metabolism in Health and Disease. Cell Metab 2017;25:27.
[38]. Aliu E, Kanungo S, Arnold GL. Amino acid disorders. Ann Transl Med 2018;6:471–471.
[39]. Seetharam B. Receptor-mediated endocytosis of cobalamin (vitamin B12). Annu Rev Nutr 1999;19:173–95.
[40]. Hall CA. Transcobalamins I and II as natural transport proteins of vitamin B12. J Clin Invest 1975;56:1125.
[41]. Sil A, Kumar H, Mondal RD, *et al.* A randomized, open labeled study comparing the serum levels of cobalamin after three doses of 500 mcg vs. a single dose methylcobalamin of 1500 mcg in patients with peripheral neuropathy. Korean J Pain 2018;31:183.
[42]. Lyon P, Strippoli V, Fang B, Cimmino L. B Vitamins and One-Carbon Metabolism: Implications in Human Health and Disease. Nutrients 2020;12:1–24.
[43]. Julian T, Syeed R, Glascow N, Angelopoulou E, Zis P. B12 as a Treatment for Peripheral Neuropathic Pain: A Systematic Review. Nutrients 2020;12:1–16.
[44]. González-Montaña JR, Escalera-Valente F, Alonso AJ, Lomillos JM, Robles R, Alonso ME. Relationship between Vitamin B12 and Cobalt Metabolism in Domestic Ruminant: An Update. Anim an Open Access J from MDPI 2020;10:1–36.
[45]. Jensen HR, Laursen MF, Lildballe DL, Andersen JB, Nexø E, Licht TR. Effect of the vitamin B12-binding protein haptocorrin present in human milk on a panel of commensal and pathogenic bacteria. BMC Res Notes 2011;4:1–6.
[46]. Surendran S, Adaikalakoteswari A, Saravanan P, Shatwaan IA, Lovegrove JA, Vimaleswaran KS. An update on vitamin B12-related gene polymorphisms and B12 status. Genes Nutr 2018;13:1–35.
[47]. Rodriguez NM, Shackelford K. Pernicious Anemia. StatPearls July 2022.
[48]. Chan CQH, Low LL, Lee KH. Oral Vitamin B12 Replacement for the Treatment of Pernicious Anemia. Front Med 2016;3:1.
[49]. Fleming SA, Gutknecht NC. Naturopathy and the Primary Care Practice. Prim Care 2010;37:119.