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Vitamin B12 in Dermatology: A Review

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ABSTRACT

The water-soluble vitamin B12, often known as cobalamin, is crucial for the haematological and neurological systems and has a complicated connection with the skin. Dermatological symptoms caused by altered cobalamin levels may point to a vitamin shortage or excess. Cobalamin's biology and metabolism are intricate, and disorders may be linked to changes in this metabolic pathway. The most frequent cutaneous signs of cobalamin insufficiency are hyperpigmentation, followed by changes to the hair, nails, and mouth, including glossitis. In addition, an excess or shortage of cobalamin has been linked to a number of dermatological disorders, such as vitiligo, aphthous stomatitis, atopic dermatitis, and acne. Acne, rosacea, allergic reactions at the injection site, and anaphylaxis are some of the cutaneous side effects of cobalamin therapy. Patients with cobalt sensitivity have been known to experience cutaneous symptoms after taking cobalamin replacement therapy because cobalt is a component of cobalamin.

INTRODUCTION

The haematological and neurological systems depend heavily on vitamin B12, sometimes referred to as cobalamin, which is a water-soluble vitamin. It is a cofactor for the enzymes

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methylmalonyl-CoA mutase and homocysteine methyltransferase, and it can take many different forms in the body. Since cobalamin is produced by bacteria and other microbes, animal products are its main source. This study examines cobalamin metabolism, diseases linked to high levels of cobalamin, clinical signs of cobalamin deficiency, relationships between cobalamin and a number of dermatological conditions, including vitiligo, aphthous stomatitis, and atopic dermatitis, as well as side effects of cobalamin therapy. In an effort to raise awareness of the different ways in which cobalamin changes might affect the diagnosis and treatment of a number of disorders, the focus is on the disease states and findings that are significant to the dermatologist.

Biochemistry of Cobalamin

The two physiologically active coenzymes that vitamin B12 takes in the body are methylcobalamin and adenosylcobalamin. Methionine synthase, a crucial enzyme in the folic acid-dependent synthesis of pyrimidines and purines, and methylcobalamin are coenzymes. Methylmalonyl CoA mutase uses adenosylcobalamin in the enzymatic breakdown of fatty acids. Both the bone marrow and the central nervous system require these enzymes to operate normally [1].

A number of coenzymes are needed for the complicated absorption and metabolism of cobalamin .When cobalamin is consumed through dietary sources, pepsin in the stomach first breaks it free from the proteins in the food. It then attaches to haptocorrin, a substance that is present in saliva that shields cobalamin from the stomach's acidic environment. When digestive proteases break down haptocorrin in the duodenum, free cobalamin attaches to intrinsic factor.

Elevated Cobalamin Levels

The term ‘elevated cobalamin levels’ refers to serum concentrations of the vitamin that are greater than 950 pg/ml (701 pmol/L). These levels can be brought on by excessive ingestion or

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administration (such as in cobalamin therapy), the release of cobalamin from an internal reservoir, and most frequently, an increase in transcobalamin (the cobalamin transporter) that results from excessive production or a lack of clearance as well as a lack of affinity for transco Numerous pathologic conditions, such as chronic myelogenous leukaemia, promyelocytic leukaemia, polycythemia vera, and hypereosinophilic syndrome, are associated with elevated cobalamin levels. Hypereosinophilic syndrome exhibits the highest cobalamin increase of these disorders. The enhanced haptocorrin production by granulocytes and their precursors is what results in the elevated cobalamin level. Since haptocorrin is not linked to secondary eosinophilia, as is the case with parasitic infections, it can be used to distinguish between primary and secondary eosinophilia [2]. Raised cobalamin levels along with elevated tryptase levels in patients with hypereosinophilic syndrome can help identify a subset of patients with a myeloproliferative version of the disease that has tissue fibrosis and a bad prognosis. The FIP1L1-PDGFRA mutation seen in these patients imparts imatinib response [5].

Deficiency in cobalamin

One of the most prevalent vitamin deficits is vitamin B12, however there is no agreed-upon threshold for cobalamin, folate, holotranscobalamin, methylmalonic acid, or homocysteine levels. A recent review article revealed that the serum cut-off points for deficiency in journal articles varied widely: for cobalamin, they ranged from 100 to 350 pmol/L; for holotranscobalamin, they ranged from 20 to 50 pmol/L; for methylmalonic acid, they ranged from 0.21 to 0.470 lmol/L; for homocysteine, they ranged from 10 to 21.6 lmol/L; and for folate, they range Additionally, a transcobalamin shortage might infrequently result in cobalamin pseudo-deficiency (low cobalamin serum levels but no genuine deficiency). Methylmalonic acid and homocysteine levels would disclose this pseudodeficiency in this situation, negating the need for cobalamin therapy [8]. Measuring methylmalonic acid in the urine, which has been established to be a reliable laboratory marker in infants [9], is another technique to test for cobalamin insufficiency.

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A diagnosis of vitamin B12 deficiency can be made using results of decreased serum cobalamin, increased methylmalonic acid, or raised homocysteine .In a study of 406 patients with documented vitamin B12 insufficiency, serum levels of homocysteine and methylmalonic acid were both increased in 98.4% and 95.9% of the patients, respectively (defined as three standard deviations above the mean). There is a sensitivity of 99.8% when measuring homocysteine and methylmalonic acid levels together for diagnosis. Hematological symptoms of the cobalamin deficit were not yet seen in this investigation because 28% of the patients had normal hematocrit levels and 17% had normal mean corpuscular volumes [10]. One must also take into account the fact that a folate shortage might increase homocysteine and unintentionally lower serum levels of vitamin B12 when assessing laboratory results. Additionally, methylmalonic acid might be increased by renal illness.

Numerous genetic loci in various ethnicities have been linked to the normal variance in cobalamin and folate levels.The cobalamin absorption and metabolism pathways are affected by the gene products [12]. Cobalamin intracellular processing genetic abnormalities have been categorised into nine complementation classes. The severe effects of these mutations include homocystinuria, methylmalonic aciduria, or a combination of the two. The current prevalence of newborn screening for homocysteine and methylmalonate emphasises the value of detecting and caring for these patients early [13]. The adenosine triphosphate (ATP)-binding cassette transporter ABCD4, which is involved in the release of cobalamin from lysosomes into the cytoplasm, is the target of the most recent reported mutation [14]. This mutation has been reported to create a phenotype of skin pigmentation, in contrast to the other mutations, which cause severe phenotypes with few discernible skin findings. One example had a 14-year-old boy who had hyperpigmentation combined with neurological problems [15], while another involved a 12-year-old girl who had diffuse progressive skin pigmentation without neurological or cardiovascular consequences [16].

Clinical signs of extracutaneous cobalamin insufficiency can take many different forms. Megaloblastic macrocytic anaemia with hypersegmented polymorphonuclear cells and pancytopenia are examples of haematological symptoms. Paresthesias, peripheral neuropathy,

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and integrated systems illness with demyelination of the dorsal columns and corticospinal tract are examples of neurological symptoms. Irritability, personality changes, minor memory loss, dementia, depression, and psychosis are examples of psychiatric alterations.An assessment of the serum levels of folate and cobalamin should be taken into consideration because cobalamin insufficiency has been reported frequently to manifest with parasitosis delusions [18].

Cutaneous Manifestations of Cobalamin Deficiency

The oral cavity, palms, soles, and flexural areas are particularly affected by the global hyperpigmentation pattern. Additionally, pressure points like the terminal phalanges, knees, and elbows may make it more noticeable. The first sign of a vitamin B12 deficiency may be hyperpigmentation [21].Linear streaks on the nails and hair changes, such as polio, are also visible [22]. When using replacement treatment, these results typically change over several months.

Increased melanin in the basal layer of the epidermis supports the pathologic diagnosis of hyperpigmentation resulting from vitamin B12 insufficiency. Numerous melanosomes were observed in melanocytes and their surrounding keratinocytes in one electron microscopy examination. According to this study, an increase in melanin production is the primary mechanism causing hyperpigmentation brought on by vitamin B12 deficiency [23]. A biopsy revealed a greater number of cutaneous blood vessels in one patient with reddish hyperpigmentation caused by chronic cobalamin insufficiency that was treated with vitamin B12 injections. Vascular endothelial growth factor had weak expression in the pathology, which may have encouraged angiogenesis in this patient and could be a mechanism for the hyperpigmentation caused by cobalamin deficiency [24]. Additionally, it has been hypothesised that the rise in melanin may be caused by cobalamin's effect on the level of reduced-type glutathione, which typically inhibits tyrosinase [16].

Dermatologic Disease Associations with Cobalamin Deficiency

Cobalamin deficiency can present as vitiligo, however in the majority of instances, neither condition is accompanied by the other. Because of this, it might be challenging to decide whether

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cobalamin insufficiency should be looked into in people who have vitiligo. In a group of 69 patients with vitiligo and 52 people in the control group, Karadag et al. [16] evaluated numerous serum markers of cobalamin insufficiency, including cobalamin, folic acid, homocysteine, and holotranscobalamin. They discovered that the vitiligo group had lower levels of vitamin B12 and holotranscobalamin, which is regarded as the early sign of shortage, and greater levels of homocysteine and haemoglobin. Their team hypothesised that the connection could be a result of patients with cobalamin deficiency, hyperhomocysteinemia, and vitiligo sharing a similar genetic origin. The results of two earlier research that looked into the connection between high homocysteine levels and vitiligo were contradictory.

While Balci et al. [18] observed no significant difference in the levels of homocysteine between 48 patients with vitiligo and the control group, Shaker and El-Tahlawi [17] demonstrated that homocysteine levels were considerably higher in 26 patients with vitiligo than in healthy controls.Similar to that, studies using cobalamin as a treatment for vitiligo have produced conflicting results.

Atopic Dermatitis

Even in cases where there is no clinical or subclinical insufficiency, cobalamin has been utilised to treat a variety of dermatological conditions [14]. Cobalamin applied topically has demonstrated potential as a secure treatment for atopic dermatitis. An 8-week trial using 0.07% cyanocobalamin cream on one side of the body and a vehicle on the other involved 49 patients with atopic dermatitis. The cyanocobalamin cream was well tolerated by the patient and appeared to be effective from the investigators' and patient's perspectives. The modified Six Area Six Sign Atopic Dermatitis score, which accounts for itchiness, erosion, lichenification, erythema, and infiltration, was applied. In this study, the treatment side's score decreased by a substantial amount more than the placebo side's score (55.34 for the vitamin B12 cream vs. 28.87 for the placebo) [15].

Complications of Vitamin B12 Therapy

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Cobalamin is already widely used to treat cobalamin deficiency, despite showing promise in the treatment of several dermatologic disorders. The dermatologist must be aware of the potential dermatologic side effects that may complicate cobalamin therapy. There have been multiple cases of people receiving intramuscular cobalamin injections developing monomorphic acneiform outbreaks. After the therapy was stopped, the eruptions went away [18]. It has been shown that the vitamins cyanocobalamin, pyridoxine (B6), and riboflavin (B2) aggravate already present acne [18]. A 17-year-old female developed rosacea fulminans after receiving supra-therapeutic doses of oral vitamin B12 and B6 at 4,000 and 2,000% of the recommended daily allowance, respectively [19]. Both parenteral and intramuscular cobalamin have been associated with allergic and anaphylactic responses. Although they have happened with both of the forms that are now available, cyanocobalamin and hydroxycobalamin, with some individuals displaying crossreactivity to both [20, 21], they are more frequent with cyanocobalamin. It is a suitable treatment to switch individuals who are exclusively sensitive to cyanocobalamin to hydroxycobalamin [22]. Kartal et al. [23] were able to desensitise a patient who had become sensitive to both formulations in one instance.

Patients can lower their intake of dietary cobalt by using the point-based system suggested by Stuckert and Nedorost [16]. It should be noted that dental implants include a growing proportion of cobalt, which can lead to oral hypersensitivity and a strong burning sensation in the mouth [24]. Since nickel allergies are frequently related to cobalt sensitivity, finding out about them before beginning vitamin B12 therapy may be beneficial [25-26]. Commercially available spot tests for cobalt are crucial for determining skin exposure and the health hazards linked to metal exposures (e.g., http://www. smartpractice.com) [19].

CONCLUSION

A deficit of cobalamin is very common as people get older because it is necessary for the body to function properly. By identifying the mucocutaneous signs of the deficit, the dermatologist can assist in the diagnosis. Since many patients are receiving cobalamin

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medication, it's particularly critical to understand cutaneous side effects. Cobalamin has been linked to dermatological conditions such vitiligo, atopic dermatitis, and aphthous stomatitis. Advances in diagnosis and treatment could result from a better understanding of the precise interactions between these diseases and cobalamin.

Acknowledgments

REFERENCES

1. Andre`s E, Serraj K, Zhu J, Vermorken AJ. The pathophysiology of elevated vitamin B12 in clinical practice. QJM.2013;106(6):505–15.

2. Klion AD, Robyn J, Maric I, Fu W, Schmid L, Lemery S, Noel P,Law MA, Hartsell M, Talar-Williams C, Fay MP, Dunbar CE,Nutman TB. Relapse following discontinuation of imatinib mesylate therapy for FIP1L1/PDGFRA-positive chronic eosinophilic leukemia: implications for optimal dosing. Blood. 2007;110(10):3552–6.

3. Leiferman KM, Gleich GJ, Peters MS. Dermatologic manifestations of the hypereosinophilic syndromes. Immunol Allergy Clin North Am. 2007;27(3):415.

4. Aparicio-Ugarriza R, Palacios G, Alder M, Gonza´lez-Gross M. A review of the cut-off points for the diagnosis of vitamin B12 deficiency in the general population. Clin Chem Lab Med. 2014(Epub ahead of print).

5. Adcock BB, McKnight JT. Cobalamin pseudodeficiency due to a transcobalamin I deficiency. South Med J. 2002;95(9):1060–2.

6. Kalay Z, Islek A, Parlak M, Kirecci A, Guney O, Koklu E, Kalay S. Reliable and powerful laboratory markers of cobalamin deficiency in the newborn: plasma and urinary methylmalonic acid. J Matern Fetal Neonatal Med. 2014 (Epub ahead of print).

7. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. Am J Med. 1994;96:239–46.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 6, Sep 2022

8. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician.2003;67(5):979–86.

9. Grarup N, Sulem P, Sandholt CH, Thorleifsson G, Ahluwalia TS, Steinthorsdottir V, Bjarnason H, Gudbjartsson DF, Magnusson OT, Sparsø T, Albrechtsen A, Kong A, Masson G, Tian G, Cao H, Nie C, Kristiansen K, Husemoen LL, Thuesen B, Li Y, Nielsen R, Linneberg A, Olafsson I, Eyjolfsson GI, Jørgensen T,Wang J, Hansen T, Thorsteinsdottir U, Stefa´nsson K, Pedersen O.

10.Genetic architecture of vitamin B12 and folate levels uncovered applying deeply sequenced large datasets. PLoS Genet. 2013;9(6):e1003530.

11. Froese DS, Gravel RA. Genetic disorders of vitamin B12 metabolism: eight complementation groups- eight genes. Expert Rev Mol Med. 2010;12:e37.

12. Coelho D, Kim JC, Miousse IR, Fung S, du Moulin M, Buers I, Suormala T, Burda P, Frapolli M, Stucki M, Nu¨rnberg P, Thiele H, Robenek H, Ho¨hne W, Longo N, Pasquali M, Mengel E,Watkins D, Shoubridge E, Majewski J, Rosenblatt D, Fowler B,Rutsch F, Baumgartner M. Mutations in ABCD4 cause a new inborn error of vitamin B12 metabolism. Nat Genet. 2012;44:1152–5.

13. Kim JC, Lee NC, Hwu PW, et al. Late onset of symptoms in an atypical patient with the cblJ inborn error of vitamin B12 metabolism: diagnosis and novel mutation revealed by exome sequencing. Mol Genet Metabol. 2012;107:664–8.

14. Takeichi T, Hsu CK, Yang HS, Chen HY, Wong TW, Tsai WL, Chao SC, Lee JY, Akiyama M, Simpson MA, McGrath JA. Progressive hyperpigmentation in a Taiwanese child due to an inborn error of vitamin B12 metabolism (cbIJ). Br J Dermatol. 2014 (Epub 2014 Sep 18).

15. Chiang TT, Hung CT, Wang WM, Lee JT, Yang FC. Recreational nitrous oxide abuse-induced vitamin B12 deficiency in a patient presenting with hyperpigmentation of the skin. Case Rep Dermatol. 2013;5(2):186–91.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 6, Sep 2022

16. Tjioe M, Gerritsen MJ, Juhlin L, van de Kerkhof PC. Treatment of vitiligo vulgaris with narrow band UVB (311 nm) for one year and the effect of addition of folic acid and vitamin B12. Acta Derm Venereol. 2002;82(5):369–72.

17. Kozlak ST, Walsh SJ, Lalla RV. Reduced dietary intake of vitamin B12 and folate in patients with recurrent aphthous stomatitis. J Oral Pathol Med. 2010;39(5):420–3.

18. Volkov I, Rudoy I, Freud T, Sardal G, Naimer S, Peleg R, Press Y. Effectiveness of vitamin B12 in treating recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled trial.J Am Board Fam Med. 2009;22(1):9–16.

19. Karadag AS, Tutal E, Ertugrul DT, Akin KO. Effect of isotretinoin treatment on plasma holotranscobalamin, vitamin B12, folic acid, and homocysteine levels: non-controlled study. Int J Dermatol.2011;50(12):1564–9.

20. Volkov I, Press Y, Rudoy I. Vitamin B12 could be A ‘master key’ in the regulation of multiple pathological processes. J NipponMed Sch. 2006;73:65–9.

21. Stu¨cker M, Pieck C, Stoerb C, Niedner R, Hartung J, Altmeyer P.Topical vitamin B12—a new therapeutic approach in atopic dermatitis—evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. Br J Dermatol. 2004;150:977–83.

22. Yamashiki M, Nishimura A, Kosaka Y. Effects of methylcobalamin (vitamin B12) on in vitro cytokine production of peripheral blood mononuclear cells. J Clin Lab Immunol. 1992;37(4):173–82.

23. Bilwani F, Adil SN, Sheikh U, Humera A, Khurshid M. Anaphylactic reaction after intramuscular injection of cyanocobalamin (vitamin B12): a case report. J Pak Med Assoc. 2005;55(5):217–9.

24. Tordjman R, Genereau T, Guinnepain MT, Weyer A, Lortholary O, Royer I, Casassus P, Guillevin L. Reintroduction of vitamin B12 in 2 patients with prior B12-induced anaphylaxis. Eur J Haematol. 1998;60(4):269–70.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 6, Sep 2022

25. Moloney FJ, Hughes R, O'Shea D, Kirby B. Type I immediate hypersensitivity reaction to cyanocobalamin but not hydroxycobalamin. Clin Exp Dermatol. 2008;33(4):412–4.

26. Kartal O, Gulec M, Demirel F, Yesillik S, Caliskaner Z, Sener O.Vitamin B12 allergy and successful desensitisation with cyanocobalamin: a case report. Allergol Immunopathol. 2012;40(5):324–5.