Review

Role of vitamin B12 in treating recurrent aphthous stomatitis: A review

Rim Taleb, Bassel Hafez, Nadim El Kassir, Hani El Achkar, and Mohamad Mourad

Faculty of Medicine, Beirut Arab University, Beirut, Lebanon

Abstract: Vitamin B12, a water-soluble vitamin, plays a vital role in the formation of hematopoietic stem cells and has been associated with oral mucosal diseases, mainly recurrent aphthous stomatitis (RAS). The latter is a debilitating condition, and B12 was proposed as a potential treatment given its role in regenerating oral mucosal tissue. There is conflicting evidence that B12 deficiency causes RAS. Five of the seven randomized controlled trials reviewed used the inactive form of B12 (cyanocobalamin) as intervention, while the other two used the active form (methylcobalamin). Of the latter two, buccal discs (500 μg B12) showed significant improvement and reduced perceived pain in 77% of the subjects, and submucosal injections showed a significant difference in pain, starting from the second day. Moreover, three studies administered vitamin B12 sublingually with different dosages, which revealed that the higher dose (1000 μg) achieved a significant reduction in outbreaks, number, and duration of ulcers, especially after six months. Multivitamins showed no difference in new RAS episodes and duration. Injectable B12 was compared with the oral form, and nearly 50% of the injection group reported a desired response by the eighth week. An ointment form (500 μg) showed a significant reduction in pain levels after two days of treatment. Based on the available literature, we suggest that a daily dose of 1000 μg of vitamin B12 sublingually for six months can be used to treat RAS. Nevertheless, this conclusion should be considered tentative due to the lack of high quality, large scale studies.

Keywords: Vitamin B12, recurrent aphthous stomatitis, RAS, review

Introduction

Vitamin B12, also known as Cobalamin, is a water-soluble vitamin primarily found in animal products. It is of importance in the formation of hematopoietic cells. When a vital step in folate or homocysteine/methionine cycles is impeded, metabolic intermediates, homocysteine, and methylmalonic acid (MMA) accumulate. MMA accrues in response to vitamin B12 deficiency, while elevations in homocysteine concentration indicate a dual deficiency in vitamin B12 and folate. Intracellular vitamin B12 is metabolized into adenosylcobalamin or methylcobalamin and both these forms act as cofactors for enzymes, most importantly; methionine synthase and methylmalonyl-CoA (Coenzyme A) mutase. Homocysteine is metabolized by remethylation to produce methionine and this reaction is catalyzed by methionine synthase; with methylcobalamin as a cofactor. Moreover, adenosylcobalamin is a cofactor in the synthesis of succinyl-CoA from methylmalonyl-CoA which is catalyzed by methylmalonyl-CoA mutase. Tetrahydrofolate (THF) participates in homocysteine but not in the metabolism of MMA. Therefore, B12 deficiency is associated with elevations in serum levels of both homocysteine and MMA, while only homocysteine levels are elevated in folate deficiency [1, 2].

Correlations between vitamin B12 deficiency and oral mucosal manifestations have been proposed in the past. For instance, hyperhomocysteinemia has been demonstrated to induce thrombosis in arterioles supplying the oral mucosa. Such thrombi are followed by ulcer formation. As such, vitamin B12 deficiency may play a role in the pathogenesis of recurring aphthous ulcers [3, 4]. Another possible mechanism of pathogenesis faults the high sensitivity of the rapidly dividing gastrointestinal cells to deficiencies of both vitamin B12 and folic acid as a cause [1, 4]. Indeed, the appearance of linear atrophic lesions on oral mucosa as an early diagnostic sign of vitamin B12 deficiency has been previously proposed [2, 5]. Nevertheless, the mechanism by which vitamin B12 deficiency engenders aphthous stomatitis remains unclear (Figure 1) [4–9].

Cobalamin and holotranscobalamin are two endogenous forms of vitamin B12, with the latter being the active plasma form. Vitamin B12 deficiency is associated with a vast number of clinical manifestations, including anemia symptoms such as fatigue, irritability, and others, neuropsychiatric symptoms such as depression, insomnia, forgetfulness, and others, and gastrointestinal symptoms such as glossitis.

Cyanocobalamin and hydroxocobalamin are both synthetic forms of vitamin B12 and both are used in the treatment of vitamin B12 deficiency. However, a significant

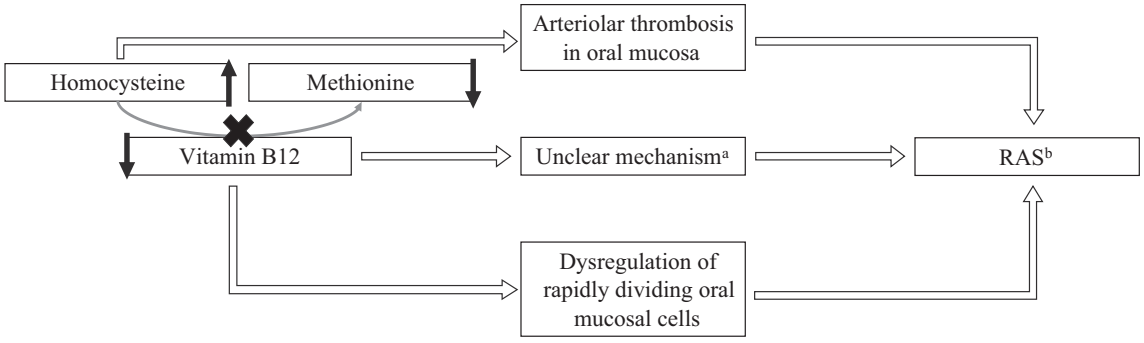

Figure 1. Relation between Vitamin B12 and RAS. [a]Although the mechanism causing RAS remains unclear, two main mechanisms were proposed as a result of hyperhomocysteinemia resulting from B12 deficiency, arteriolar thrombosis and alteration of cell division in the oral mucosa. [b]RAS: recurrent aphthous stomatitis.

difference in their administration is their maintenance dose interval. Cyanocobalamin, which contains a cyanide group, is administered on a monthly basis, whereas hydroxocobalamin is given every two-to-three months. For that reason, hydroxocobalamin was preferred over cyanocobalamin as first-choice therapy in vitamin B12 deficiency. The administration routes are various, including oral, sublingual, intramuscular (IM), intranasal, intravenous, and deep subcutaneous formulations, with parenteral administration usually reserved for severe cases of deficiency in practice. However, a Cochrane review in 2018 has concluded that low-quality evidence suggests oral and IM vitamin B12 have similar effects regarding normalizing serum vitamin B12 levels, with an advantage for oral treatment being less expensive [10].

Search strategy

We searched different online databases: MEDLINE, PubMed, Google Scholar, UpToDate, and ScienceDirect. In MEDLINE, we used the "Advanced Search" option, choosing the English Language from 1950 to the present, based on the following search strategy:

- [B12 OR Cobalamin] AND [aphthous ulcer OR aphthous stomatitis OR RAS OR RAU].
- We searched the other databases using the keywords mentioned above.

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS), also known as Canker sores [5, 7, 11], is a chronic inflammatory condition confined to the oral mucosa. Such sores may appear in singular or multiple, round, or ovoid forms while having yellow or grey floors surrounded by erythematous borders [8, 11–15]. These oral lesions are the most commonly observed kind in primary care. Prevalence rates differ in the literature, with an estimated 5–25% of the general population suffering from it at some point in their lives [12, 13, 16–18]. This wide range is due to differences between the regions and the socio-economic groups evaluated [14]. Furthermore, a recurrence of such lesions every three months in 50% of patients has been observed [19, 20].

Despite the numerous classifications of RAS, Stanley's one in 1972 remains most popular and widespread [12]. His classification of RAS is divided into three distinct types: minor, major, and herpetiform. Such demarcations of form are according to their number, size, duration, site, and healing process.

Minor RAS

The minor form of RAS referred to as Mikulicz' Aphthae, is most common, affecting 75–85% of RAS patients. These ulcers (<10 mm) may be present singularly or in a group, while being round or ovoid. In terms of location, they are primarily found in the non-keratinized mucosa of the mouth's labia and floor. However, the hallmark of this RAS form is a necrotic center covered by a yellow-gray pseudomembrane. Furthermore, these ulcers heal within two weeks, devoid of residual scarring [11–14, 18, 19].

Major RAS

Also known as Sutton disease, the major form of RAS is the second most common type, affecting approximately 10% of RAS patients. This subtype presents with multiple ulcers that may merge into more extensive irregular ulcerations. Hence, they are very similar to the minor variant; yet, larger (>10 mm). Additionally, it may affect the entire oral cavity, predominating in the lips, soft palate, and oropharynx. However, in contrast with the minor form, healing time may persist up to six weeks. Furthermore, these larger lesions leave behind a residual scar [12].

Herpetiform RAS

The herpetiform is the least common of the three, affecting 5–10% of RAS patients. Smallest in terms of size, this subtype is characterized by multiple pinpoint ulcers (<5 mm in diameter). These ulcerations may reach up to a hundred in number at any given time. Furthermore, the herpetiform subtype is considered to be the most painful of the three. In terms of location, lesions may appear anywhere in the oral mucosa, healing within two weeks without scarring [12–14].

It must be stressed that RAS nomenclature should be reserved for recurring ulcers in the absence of comorbid systemic disease [11, 17].

Diagnosis of RAS

Diagnosis is reliant primarily on history taking and physical exam [17, 19, 20]. Patients typically present to the clinic with complaints of recurrent ulcers commencing since childhood [11]. During history taking, secondary causes can be usually ruled out [21]. Many experts believe that observing a complete blood count (CBC), measuring vitamin B12 levels, and noting other hematinic deficiencies is essential. However, evidence in support of such a supposition is lacking. Then again, Belenguer-Guallar et al. advise full laboratory testing of adults with sudden outbreaks of RAS, including vitamin B12, to rule out possible secondary causes [13]. In addition, a biopsy is considered in the diagnostic workup to rule out mucocutaneous diseases and malignancies, and when the lesions persist for more than three weeks [11, 21].

Although the exact etiology of RAS is unknown, many environmental factors have been indicated in the induction of RAS. Such factors include hormonal changes, stress, trauma, drugs, food hypersensitivity, immunological factors, hereditary predisposition, and nutritional deficiencies in iron, ferritin, and vitamin B12 [15]. In the case of vitamins, previous research has suggested vitamin replacement as an alleviating factor against the recurrence of RAS, with some advocating it for primary treatment [19].

This review mainly focuses on the role of vitamin B12 in the management of RAS.

Role of vitamin B12 in the management of RAS

Brachmann suggested the possible role of vitamin B12 deficiency in the occurrence of RAS in 1954 [22]. Since then, and despite its position as a predisposing factor for RAS, investigations of the utility of vitamin B12 for management are scarce. Seven randomized controlled trials (RCTs) have been published so far. In each of these studies, several factors, including dose, route, and duration of vitamin B12 administration, were tested. Conclusive in their results, almost all investigations accepted that prescription of vitamin B12 reduced the relapse of RAS, as well as its associated pain and duration (Table 1) [7, 19, 20, 23–26]. It should be noted that the outcomes of these RCTs did not rely on the initial plasma concentrations of vitamin B12, resulting in candidates with normal or deficient vitamin B12 levels benefiting from treatment [18–20, 27].

Burgess and Haley (2008), Volkov et al. (2005, 2009), as well as Liu and Chiu (2015) studied and observed the effects of vitamin B12 for pain and ulceration, finding both were relieved upon B12 administration. Volkov et al.'s original study in 2005 included three patients complaining of RAS. During the first phase of treatment, under observation, patients were started on 1000 μg of parenteral vitamin B12 (twice a week over six weeks). The first phase was followed by a second interval of treatment, with injections administered once a month for a year. A six-month follow-up of all three patients showed successful use of vitamin B12 in the treatment of RAS [16]. Relying on previous experience, Volkov et al. later underwent another study with a greater sample size and a different administration route. Thirty-one of 58 candidates were given 1000 μg of sublingual vitamin B12 daily for six months, focusing on pain management, duration of the episode, and average number of lesions per month. Within 5–6 months of the administration, all three outcomes of disease were found to be significantly improved (as compared to the control group) ($p < 0.05$). Furthermore, their latter study observed a significant proportion of patients achieving a "no aphthous ulcer status" (74.1%) ($p < 0.01$) [20]. This study proved convenient to patients as the method was inexpensive, simple, and had no significant adverse effects. More so, many aspects of RAS were evaluated, and all three primary outcomes (pain, duration, and number of lesions) significantly decreased.

Instead, Liu and Chiu used a vitamin B12 ointment, which was given to each patient four times per day. They were a total of 42 patients, and the intervention group received the treatment for one week. Patients' pain levels were compared to their baseline levels, and results showed that these patients experienced an improvement in pain levels after two days of treatment ($p < 0.001$) [24]. The study evaluated only one outcome: the pain levels. However, it failed to show if any recurrences occurred. Additionally, it was demonstrated as adjunctive therapy with easy administration over a brief period.

Burgess and Haley (2008) performed a trial in which patients in the intervention group were treated with

Table 1. Randomized controlled trials on vitamin B12 and RAS

Articles	Number of participants	Intervention	Route of administration of B12	Duration	Results
Lalla RV, Choquette LE, Feinn RS, Zawistowski H, Latortue MC, Kelly ET, et al. Multivitamin therapy for recurrent aphthous stomatitis: a randomized, double-masked, placebo-controlled trial. J Am Dent Assoc (1939). 2012;143(4): 370-6.	160 adults	Treatment arm: Once-daily multivitamin containing 100% of the reference daily intake (RDI)* of essential vitamins Control Arm: Once-daily placebo	Orally	1 year (3 visits: baseline, 6 month, and final visit at 1 year)	• No significant difference in the mean number of new RAS episodes between both groups during the study period (P = 0.69) • No significant difference with regard to mouth pain (P = 0.60)
Qazi J. Vitamin B12 for the treatment of recurrent aphthous stomatits. JKCD. 2011;1(2):87–90.	65 patients	One group received 500 μg and the other group received 1000 μg of B12	Sublingual at bedtime	6 months	The group receiving 1000 μg all (100%) reported relief, while only 30% of patients who received 500 μg reported relief
Volkov I, Rudoy I, Freud T, Sardal G, Naimer S, Peleg R, et al. 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.	58 patients	1000 μg of B12 in the intervention group and placebo in the control group	Sublingual	6 months	• Significant reduction in the duration of outbreaks, number of ulcers, and the level of pain at 5th and 6th months regardless of the initial levels of B12 (P < 0.05) • During the last month, 20 patients (74.1%) from the intervention group and 8 (32%) from the control group reported a "No Aphthous Ulcers Status" (P < 0.01)
Rasi A, Zamanian A, Mehran G, Ezati A, Rastin V, Karimi S. Comparing the Effect of Injectable Vitamin B With Conventional Oral Treatment on Aphthous Stomatitis. J Skin Stem Cell. 2018;5(1–2):e69052.	60 patients	Group received injectable Vitamin B (a combination of B1 (100 μg), B6 (100 μg), and B12 (1000 μg)	Injectable form for the first group	8 weeks treatment, follow-up at 10 months	• Injectable form showed a better effect in terms of reduction of recurrence, number of lesions and the time of recovery of lesions at 8th and 10th week (P < 0.001) compared to the oral group
		Other group received Chewable tablets (a combination of iron (1 tablet), folic acid (1 tablet), involved daily intake of vitamin B complex tablet (including B1, B2, B6 and nicotinamide) and Vitamin C (250 μg tablet)	Oral chewable tablets for the second group		• In the Injection group, nearly 47% reported a desired response, 40% reported a moderate response and 13% reported a weak response (P < 0.001)
Liu H-L, Chiu S-C. The effectiveness of vitamin B12 for relieving pain in Aphthous ulcers: a randomized, double-blind, Placebo-controlled Trial. Pain Manag Nurs. 2015; 16(3):182-7.	42 patients	500 μg of vitamin B12 ointment	Ointment	1 week	• Significant difference in pain levels after 2 days of treatment was found between the intervention and the control groups (P < 0.001)
		Placebo ointment (same ingredients except for B12)			• Mean visual analog scale, 0.36 [95% CI, 0.01–0.71] vs. 1.80 [1.16–2.44]; (P < 0.001)

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Table 1. (Continued)

Articles	Number of participants	Intervention	Route of administration of B12	Duration	Results
Burgess J, Haley J. Effect of bioactive B12 in adhering discs on aphthous ulcers. Inside Dent. 2008;4(9):60–4.	26 patients	500 μg disc daily before bedtime	Discs, buccal	30 days	Significant improvement reported in 77% of the patients ($P < 0.03$) and reduced perceived pain ($P < 0.02$) in the intervention group with no adverse reactions noted
Golestannejad Z, Ghalayani P, Mojtahedi N, Foroughi A. The effectiveness of submucosal injection bioactive vitamin B12 in comparison to triaminolone in pain and frequency of apthous ulcer. ann dent spec. 2017;5(3):122.	40 patients	Intervention group received 0.1 cc/cm^2 of methylcobalamin Control group received 0.1 cc/cm^2 of Triamcinolone	Submucosal Injections	9 days	• Significant reduction in pain in the intervention group from the 3rd till the 6th day ($P < 0.05$) along with recovery time ($P < 0.001$) • From the 7th day till the 9th day there was a difference in pain between the two groups but not statistically significant ($P > 0.05$)

*RDI: Reference daily intake.

500 μg discs of vitamin B12 once daily over 30 days. Each disc was taken before sleep, by adherence to the buccal side of a tooth. The disc would then dissolve within 20–40 minutes. In response to therapy, they reported significant improvement in 77% of patients ($p < 0.03$). Moreover, patients perceived a reduction in RAS associated pain ($p < 0.02$) as compared to the placebo group. Reduction in the frequency and duration of the ulcers occurred more in the intervention group receiving the discs; however, the small sample size was an issue.

Qazi et al. compared the daily sublingual administration of vitamin B12 (1000 μg) to oral administration (500 μg) in 65 patients, regardless of serum vitamin B12 levels. As a result of sublingual treatment, recurrence rates of RAS decreased by the fourth month, with complete relief by the sixth month in all patients. Conversely, only 30% of patients administered 500 μg tablets reported complete relief [19]. As compared to the study done by Volkov et al. in 2009, similar B12 dose and route of administration were used in the intervention, however it compared different dosages of B12 rather than with placebo, and it supported the hypothesis that higher dosage of B12 leads to better outcomes.

However, another RCT, published in 2012 by Lalla et al. did not find any measured effectiveness in multivitamin supplementation. Their study specifically depended on U. S. reference daily intake (RDI) of essential vitamins, including an estimated vitamin B12 dose of 2.4 μg. In response to multivitamin intake, RAS patients did not exhibit significant decreases in pain perception ($p = 0.60$) and cankerous episodes ($p = 0.69$) [7]. Such results were in agreement with other studies' observation of a low dosage being a less efficacious treatment. Hence, multivitamin supplementation was not advised as a treatment for RAS.

Rasi et al. compared chewable vitamin B12 efficacy to injectable administration in 60 patients divided into two groups. Oral chewable tablets contained B complex, and the injectable form had B1, B6, and 1000 μg of B12. Each was administered for eight weeks. RAS associated recurrence intervals, lesion number, and pain perception were monitored over ten months. Results were classified into three subtypes, including high efficacy (complete recovery), moderate efficacy (recurrence periods, relapse intervals, and reduced pain perception), and low efficacy (no difference in recurrence and relapse; yet, with pain reduction). After ten months, 14 of 30 patients showed a high efficacy response to injectable administration. Inversely, none of the patients who received oral doses demonstrated high efficacy responses. However, both groups showed similar moderate efficacy rates, with 12 of 30 patients responding to injectable vitamin B12, and 9 of 30 patients responding to the oral administration. Nine of 30 patients did not show any response to oral treatment. Thus, this study confirmed a better response to the injectable form of 1000 μg vitamin B12 compared to the chewable form. Nevertheless, the study has issues that need to be clarified, mainly the dose of vitamin B12 in the chewable tablet, and the exact route of the injectable form (intramuscular, intravenous, submucosal, or subcutaneous) [23].

Wray et al. tested the use of intramuscular (IM) injections of hydroxocobalamin (1000 μg) every two months for a year, in 1975. The study was conducted on 130 RAS patients. Twenty-three patients had deficiencies in iron, folic acid, or vitamin B12, of which fifteen completely recovered and

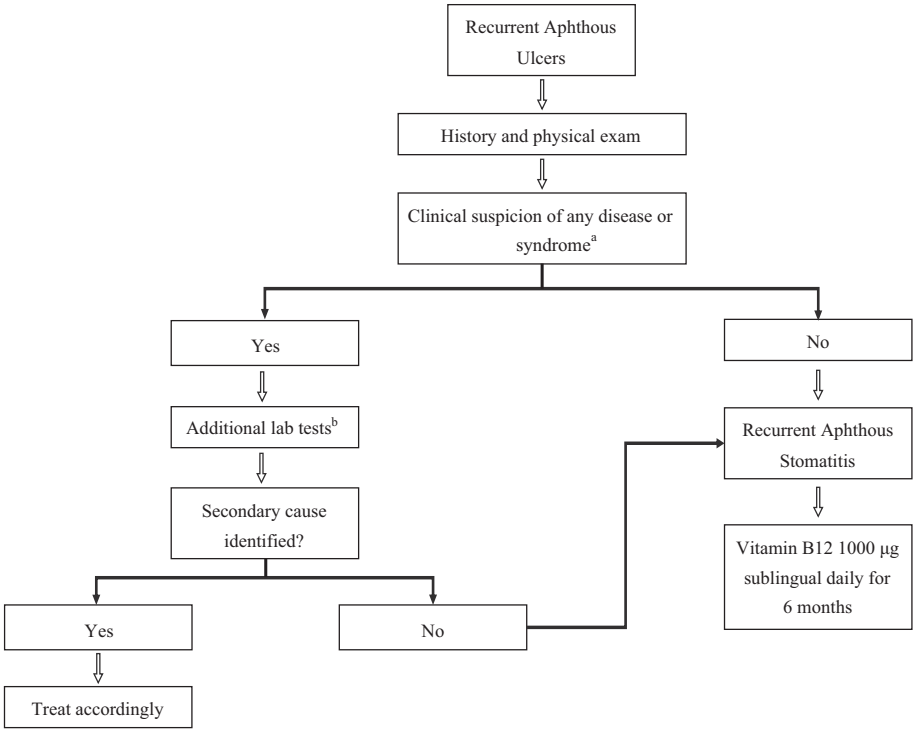

Figure 2. Algorithm for the management of Recurrent Aphthous Ulcers. [a]Differential diagnosis of recurrent aphthous ulcers includes Behçet's disease, Crohn's disease, systemic lupus erythematosus, nutritional deficiencies, and others. [b]Lab tests include: complete blood count (CBC), blood smear, serum levels of vitamin B12 (not routinely done), and other lab tests based on clinical evaluation.

eight exhibited improvement ($p < 0.001$). It is to note that RAS patients with deficiencies in iron and folate showed improvement to IM administration [6].

Gulcan et al. (2008) compared the correlation between RAS and Cobalamin deficiency and tested IM injections in their study, using 1000 µg/day for the first seven days, then once a week for a month and finally once every month for six months. They noted a significant recovery of 96% of their patients ($n = 69$) with a lack of recurrent episodes ($p < 0.001$). They recommended that any patient who suffers from RAS should have a serum cobalamin level of more than 500 pg/mL to achieve mucosal protection and prevent future episodes [27].

Golestannejad et al. had a different approach to their intervention, using a submucosal injection instead of a systemic form. Furthermore, the injection contained the active form of vitamin B12 (methylcobalamin 0.1 cc/cm^2) instead of the inactive cyanocobalamin. The results of their study suggested a higher efficacy in treating with methylcobalamin when compared to triamcinolone therapy, observing reduced pain perception ($p < 0.05$) and recovery time after three days of administration ($p < 0.001$) [26]. However, the latter study has multiple concerns regarding the short-term follow-up of patients, the need to give treatment during the episode, and the concern of compliance of patients undergoing a submucosal injection.

Collectively, these studies demonstrated that vitamin B12 is an effective therapy in treating RAS. This therapy showed multiple advantages: significantly reducing pain perception, decreasing the duration of current aphthous ulcers, and preventing recurrences. There were differences regarding the dose, route of administration, and the duration of each treatment. It is essential to know that a multivitamin tablet would not provide the dosage of B12 required to help with RAS management and was found entirely ineffective. Ointments, discs, and submucosal injections need more studies as the available data is scarce. An approach to the optimized use of vitamin B12 was made using the results of the mentioned studies (Figure 2).

Vitamin B12 deficiency and RAS

A comparison of hematinic deficiencies between RAS patients and healthy persons by Olson et al. suggested there were no significant differences between the two groups regarding vitamin B12 levels. Instead, they asserted, other than CBC, hematological testing was unnecessary in patients with RAS [28]. This perspective was shared by Scully et al. (2006), contending that morphological identification of the lesions was enough, since laboratory testing

would neither be useful in treatment nor prevention of occurrence. Although both concede that some experts believe conducting a CBC, measuring vitamin B12 levels, and other hematinic workups are helpful, both parties cite a lack of evidence in support of their efficacy [11]. Other researchers, such as Lalla et al., are against further hematological testing, alluding to the invasiveness and costliness of such tests [7].

Indeed, serum levels of vitamin B12 tested in patients with RAS were found to be the only deficiency worthy of note compared to other hematological parameters [29, 30]. However, contrary to these recommendations, Belenguer-Guallar et al. advised further laboratory testing in adults with RAS's sudden outbreaks specific to vitamin B12 [13].

A possible relationship between vitamin B12 deficiency and RAS was first cited in the early 1950s [22]. Since then, many studies have substantiated vitamin B12's role in the pathogenesis and management of RAS. Moreover, a meta-analysis published in 2015 demonstrated how diminished levels of vitamin B12 in RAS patients, when replenished, proved beneficial in preventing recurrences of the lesion.

Combining such results demonstrates the importance of vitamin B12 in the treatment and prevention of RAS. The meta-analysis, as mentioned above, indicated multiple hematinic deficiencies, besides vitamin B12, such as folic acid, ferritin, and hemoglobin deficiencies as possible pathogenetic factors for RAS development. It was proposed that screening for these deficiencies be included in the management of such lesions [8]. Khan et al. performed a study in 2013 sampling 120 patients. They found out that a third of the participants have B12 deficiency, and 45% of RAS patients have low B12 levels. Thus, they deduced that the frequency of vitamin B12 deficiency is significant in RAS patients compared to the control group [31, 32]. In addition, other risk factors such as age and gender, along with vitamin B12, have been indicated, finding vitamin B12 deficiency to be more common in both genders aged 21–40, non-smokers, whites, high socio-economic status, and positive family history. Scully et al. discouraged using routine laboratory testing if the history and physical exam suggest the diagnosis of RAS, primarily if no other signs of a nutritional disorder or a hematinic deficiency are found. Mainly, the 2013 study supported the view that routine hematological testing should be carried out in the assessment of patients with RAS; yet, highlighted the inefficacy of multivitamin supplementation as an approach [7, 11, 33].

Conclusion

Vitamin B12 may confer clinical benefits such as decreasing the outbreaks, number, duration, and pain of RAS regardless of whether the deficiency is present or not. Based on the limited number of studies available and the different flaws in some of them, we can suggest that vitamin B12 with a dose of 1000 μg daily given sublingually for six months can be used for the treatment of RAS. The latter therapy is relatively affordable, with no significant adverse effects, and enhances patient compliance compared to injectable forms. More well-designed studies, including more participants, are required to better define a treatment strategy and improve our understanding of long-term management.

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ORCID
Rim Taleb
https://orcid.org/0000-0001-8046-3467

Rim Taleb
MD, MHPE, Senior Lecturer of Family Medicine
Faculty of Medicine
Beirut Arab University
Beirut
Lebanon
r.taleb@bau.edu.lb

