A Review of 89 Published Case Studies of Vitamin B12 Deficiency

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Abstract

Vitamin B12 (B12) is an essential nutrient needed for proper nervous system function and for the metabolism of carbohydrate, protein, and fat. Deficiencies in B12 can lead to inefficient erythropoiesis and megaloblastic anemia. The purpose of this review is to examine published case studies on vitamin B12 deficiency in adults, including a report of B12 deficiency in regards to causes, clinical manifestations, treatment/outcomes, and biomarkers of B12 status. A total of 89 applicable case studies were reviewed. Causes of B12 deficiency reported included malnutrition, lack of intrinsic factor (IF) and/or malabsorption of protein-bound vitamin B12, general malabsorption, and competition for vitamin B12. Clinical manifestations of B12 deficiency included neurological, psychiatric, oral, dermatological, and rare signs and symptoms. The majority of cases reported B12 replacement therapy via intramuscular (IM) administration. Additionally, parenteral and oral administration methods were utilized. Biomarkers of B12 status reported included serum B12 levels, mean corpuscular volume (MCV), and serum homocysteine. Serum methylmalonic acid (MMA) was also utilized in a small number of cases.

INTRODUCTION

Vitamin B12 (B12) is classified as a water-soluble vitamin, and is distinctive among all vitamins due to its large size, complexity, and that it contains the metal ion cobalt [1]. It is necessary for appropriate nervous system function and for the metabolism of carbohydrate, protein, and fat. Deficiencies in B12 can lead to inefficient erythropoiesis and megaloblastic anemia [2]. Furthermore, neurological disorders such as neuropathy, myelopathy, memory impairment, dementia, depression, and brain atrophy may occur in those with low B12 status [3]. According to one study, a neuropathy known as combined degeneration of the spinal cord, is one of the most debilitating manifestations of vitamin B12 deficiency [4]. Neurological and psychiatric symptoms have been seen in patients without related anemia or macrocytosis, with B12 concentrations in the previously defined range of low-normal. This highlights the need for the prevention of B12 deficiency [3]. The main dietary sources of B12 are animal products including meat, fish, eggs, and dairy products [3]. Other sources include B12-containing, fortified plant products such as cereals, plant-based milks, soy products, and B12-fortified yeast extract [5].

Populations at the highest risk for B12 deficiency include the elderly and those that follow a vegetarian or vegan diet. Deficiency within the elderly population is often the result of age-related gastric atrophy. This causes a decrease in acid and intrinsic factor production leading to B12 malabsorption [6]. It should be noted, however, that causes such as pernicious anemia and food-bound malabsorption account for less than half of poor B12 status among the elderly [3]. A high rate of deficiency among vegetarians or vegans exists because B12 is only naturally present in animal products, so those who do not consume diets high in fortified products are at risk [5].

The purpose of this review is to examine published case studies on vitamin B12 deficiency in adults. This will include an evaluation of B12 deficiency in regards to causes, biomarkers of B12 status, clinical manifestations, and treatment outcomes.

LITERATURE SEARCH

To identify published case studies on vitamin B12 deficiency in adults, the databases PubMed, ProQuest, ScienceDirect, and the Journal of Medical Case Reports were utilized. Searches with terms: vitamin B12 and deficiency was utilized for searches in ProQuest with “Adult” selected as the age group and “Case Study” selected as the document type. ScienceDirect searches included the terms: vitamin B12, deficiency, and case study using Journals as the content type. This was narrowed further by limiting the topics to just B12 deficiency and vitamin B12. The Journal of Medical Case Reports was searched using the terms vitamin B12, deficiency, and case study.
Searches with the terms: B12 in the title and case in the title were used for the literature searches within PubMed. Cross-referencing was employed within PubMed to identify related citations from initial search results. The total number of publications found in all databases was 353 manuscripts. After screening all publications, 89 were excluded because they were not case studies. An additional 62 were excluded as not being applicable to vitamin B12 deficiency. Seventy-eight were excluded due to not being available in English, 31 were excluded because children, adolescents, or pregnant women were described in the report, and four were excluded due to unavailability of full-text.

RESULTS

The literature search yielded a total of 89 applicable case studies, of which, 40 involved females and 49 involved males. Thirty-six cases included young adults in the age range of 18-40 years, 25 cases included those in middle adulthood aged 40-64 years, and 27 cases included elderly individuals aged 65+. One case did not report an age. Cases were reported from 28 countries in total.

The identified causes of B12 deficiency are varied, but can be grouped into four main categories. These categories are: (1) malnutrition (nutritional deficiency) (20 cases), (2) lack of intrinsic factor (IF) and/or malabsorption of protein-bound vitamin B12 (36 cases), (3) general malabsorption (8 cases), and (4) competition for vitamin B12 (nitrous oxide poisoning or metformin therapy) (11 cases) [7]. A total of 14 cases did not report a definitive cause of B12 deficiency.

Nutritional B12 Deficiency

Nutritional B12 deficiency has been attributed to cases of chronic alcoholism (1 case), and inadequate dietary intake (19 cases: 13 related to vegetarianism, 6 related to poor diet). One case of a 61 year old male with a history of excessive alcohol consumption was reported [8]. Hematological values of B12 status were not reported [8].

Thirteen cases of vegetarianism related to B12 deficiency were reported [9-20]. These cases included seven males and six females aged 18-68 years. Six of these cases reported a serum B12 level between 31.6-150 pg/mL [9-14]. Five cases reported a serum B12 level of 65.1-125.4 pmol/L [15-18] and two cases reported serum B12 levels of 101 and 195 ng/mL [19,20]. Megaloblastic anemia was indicated in three cases, [9,16,19] normocytic anemia in one case [15] and a generally defined anemia referred to as B12 deficiency anemia was indicated in one case [10]. For the mean corpuscular volumes (MCV) reported values ranged from 84-144 fl [9,13,15-17,19]. Elevated homocysteine levels were demonstrated in three cases and were 28, 30.59, and 50 µmol/L respectively [13,18,20].

Six cases of malnutrition as a result of poor or insufficient diet were reported. These included three males and three females aged 21-73 years [21-26]. Serum B12 levels of 55, 79, and 140 pmol/L were reported in three cases [21-23]. Two cases reported serum B12 levels of 35 and <100 pg/mL [24,25]. One case indicated a serum B12 level of 54 ng/L [26]. MCV levels were reported in 3 cases and were 94.3, 108 and 125 fl respectively [21,23,26]. Homocysteine was reported as 88 µmol in one case [21] and serum holotranscobalamin was reported as 27.89 pmol/L in another three cases provided information on dietary habits likely leading to deficiency. One case of a 26 year old female indicated a very poor diet of corn snacks, chips, and fast food; and no consumption of vegetables for several years [26]. A case of a 21 year old male reported a very limited diet of toasted oats cereal without milk, bread, and French-fried potatoes. The patient had aversion to many food textures including meat [21]. A case of a 73 year old male reported infrequent intake of meat, but the patient did consume fish three to four times a week [23]. All other cases did not provide specific information on dietary habits [22,24,25].

Lack of Intrinsic Factor (IF)/Malabsorption of Protein-bound B12

Thirty-six cases reported B12 deficiency due to lack of IF or other causes of malabsorption of protein-bound B12. These included 22 males and 14 females ranging in age from 22 to 87 years [27-56]. Their serum B12 levels ranged from 5-307 pg/mL [27-45], 51-338 ng/mL [46-52] and 25-104 pmol/L [53-56]. Of MCV levels reported, values ranged from 80-122 fl [27,29,31,32,34] [36,39,41,43,44,46,54,56]. Homocysteine levels were reported in nine cases total ranging in six cases from 23-150 µmol/L [34,42,44,47,54,55]. Three cases indicated homocysteine levels at 18 ng/mL, [40] >50 nmol/L, [33] and 120 mcg/L [50].

General malabsorption

Eight cases reported general malabsorption as related to B12 deficiency. These cases included six males and two females aged 18-73 years [57-64]. Serum B12 levels ranged from 60-169 pg/mL in five cases, [57-61] and were reported as 121 ng/mL, 349 ng/mL, and 1365 pmol/L in three cases [62-64]. Seven cases reported MCV levels which ranged from 81-108 fl [57-62,64]. Two cases indicated homocysteine levels of 64.4 µmol/L and 93 µmol/L [59,64]. Additionally, methymalonic acid (MMA) was reported as 722 nmol/L in one case [63].

Malabsorption occurred in three cases as a result of bowel resection due to midgut volvulus, [57] congenital necrotizing ileus, [59] and diffuse large B cell lymphoma (DLBCL) [60]. One individual experienced malabsorption due to issues at the terminal ileum [62]. One case indicated malabsorption of B12 due to an abnormal binding protein in the serum resulting in a high serum B12 level, but very low red blood cell B12 level [64]. Moreover, one case indicated functional B12 deficiency due to a failure of intracellular transport [63]. The other two cases only indicated a generalized malabsorption with no definitive cause stated, [58,61] one of these cases, however, did indicate Klebsiella pneumonia or malabsorption from the upper GI tract as a potential cause [61].

Competition for B12

Three cases were reviewed which presented post-operative occurrences of B12 deficiency as a result of nitrous oxide exposure during surgery. This included three males aged 52, 57, and 65 years [56,65,66]. Development of deficiency symptoms occurred at 7 days [65], 16 days [66], and 2 months [65] post-operative. Serum B12 status was reported as 135 pmol/L [65]
Three studies presented cases of nitrous oxide induced vitamin B12 deficiency as a result of recreational misuse. These cases included two females and one male [67-69]. Specific age was not given in the first case but indicated that the patient was in their twenties, [67] the second case was of a 23 year old, [68] and the third was a 33 year old [69]. All patients inhaled nitrous oxide through whipped cream bulbs abusively (10-20 bulbs/day [67]); 130 bulbs/day [68], daily use for 4 weeks [69]). Serum B12 levels were 124 µmol/L, 125 pmol/L, and 202 pg/mL [67-69]. MCV levels were indicated in two cases and were 92 and 95 fl respectively [67,69]. A Homocysteine level was reported in one case and was 48.4 µmol/L [69].

Metformin-induced vitamin B12 deficiency was reported in five cases. These cases included three females and two males aged 60-82 years [70-73]. Specific age was not reported in one case [72]. Serum B12 levels were 60 pg/mL [70] 131 pg/mL, [71] 97 pmol/L [72] and 125 pmol/L [72]. One case did not report the serum B12 level for the patient [73]. MCV levels were indicated in three cases and were 99.7, 104, and 120.3 fl respectively [71,72].

Unreported causes

A total of 14 cases did not report a definitive cause of B12 deficiency. These cases included six males and eight females aged 31-88 years [15,17,74-83]. Serum B12 levels were reported as ranging from 13.5-247 pg/mL [45,51,74-80] and 44-113 pmol/L [15,17,81,82]. One case indicated a serum B12 level of 60 ng/L [83]. MCV levels were reported in eight cases and ranged from 65.5-114.1 fl [15,51,74,76,78-80,83]. Homocysteine levels were indicated in three cases and were 12.3 µmol/L [51] and >50 µmol/L [45,81].

CLINICAL MANIFESTATIONS

Neurological impairments

A total of 43 cases involved patients with B12 deficiency-related neurological impairment. These patients ranged from 19-82 years of age and presented an array of symptoms (Table 1). A common clinical manifestation experienced by patient’s studied with neurological impairment is paresthesia or tingling, numbness, and/or burning in the skin, which was indicated in 27 cases [19,20,21,31-34,37,38,41,45-49,53,58,49-63,53,58,63-65,68,70,73,75,76]. Another prevalent clinical manifestation observed is ataxia or the lack of coordination of muscle movements, often accompanied by gait abnormalities. This was reported in 22 cases [13,18,21,31,37,38,41,45,46,49,50,51,55,62-67,78,79]. Other symptoms commonly reported included weakness (13 cases) [19,21,34,37,42,45,46,62,64,65,68,72,75] and impaired cognitive abilities (9 cases) [13,18,31,33,37,51,66,72,79]. Four cases indicated that Lhermite’s sign, an electrical sensation which moves down spine, was a prevalent symptom especially during neck flexion [32,45,64]. Three cases reported fatigue as a problematic occurrence [48,49,79].

Psychiatric abnormalities

A total of 16 cases involved patients with B12 deficiency-related psychiatric abnormalities. These patients ranged in age 23-78 years and exhibited a multitude of symptoms (Table 2). The most prevalent features of patients experiencing psychiatric abnormalities as a result of B12 deficiency included, delusions (5 cases) [39,40,60,61,69], irritability (5 cases) [14,40,43,59,77] and decreased interest (5 cases) [11,12,25,40,60]. Other manifestations included depression (4 cases) [12,25,39,60] and sleep disturbances (4 cases) [12,25,60,74]. Symptoms such as confusion (3 cases), [39,40] fatigue (3 cases), [12,25,60] irrational behavior (3 cases) [22,69,77] and paranoia (3 cases) [40,59,74] were also observed. Hyperactivity, sexual indiscretion, social withdrawal, forgetfulness, and psychotic episodes were also seen in two cases each [43,77,11,74,22,14,59,40]. Lastly, a hallucination was a reported symptom in one case [82].

Oral manifestations

Thirteen cases reported oral manifestations of B12 deficiency, and included patients aged 19-88 years. These patients experienced varying symptoms outlined in (Table 3). The most prevalent symptoms were glossitis (4 cases) [56] recurrent aphthous stomatitis (4 cases) [15,30] and pain and burning sensations in the mouth [16,23,52,83]. Additionally, increased sensitivity was another notable feature [23,52]. Other symptoms experienced included hoarseness and vocal fold palsy, [8] red stains on cheeks and tongue, [16] and epithelial dysplasia [83].

Dermatological manifestations

A total of five cases reported B12 deficiency-related dermatological manifestations. These included patients aged 25-54 years with symptoms outlined in (Table 4). Symptoms included hyperpigmentation (3 cases) [10,24,35] and skin lesions (2 cases) [17].

Rare manifestations

Ten cases presented symptoms that were not able to be categorized as neurological, psychiatric, oral, or dermatological and could be considered rare manifestations of B12 deficiency. One or more of these symptoms could potentially resign in the previously ascribed categories; however, the majority cannot be classified. The cases involved patients between the ages of 18 and 85 years, and exhibited the symptoms outlined in (Table 5) [9,26,29,44,54,57,81,80].

TREATMENT/OUTCOMES

The majority of cases reported B12 replacement therapy via intramuscular (IM) administration as the initiated treatment. A total of 59 cases utilized this method of B12 repletion, and staggered treatment approach was often utilized. This typically consisted of daily injections for a week or longer, followed by weekly injections, then monthly injections thereafter. Doses for IM B12 therapy ranged from 100 µg to 1000 µg. Nine cases indicated that B12 was administered parenterally, five at a dose of 1000 µg [15,43,45] (3 cases) one at 3000 µg, [13] and three unreported doses [38,75,76]. One case reported intravenous and IM B12 therapy [58]. Three cases indicated that oral B12 was given at 100 µg [52] and 1000 µg [10,82]. Fifteen cases did not report specific information regarding the method of B12 administration [26,32,39,42,50,53,59,66-68,72,73,78].

Treatment with B12 replacement therapy resulted in full recovery in 40 cases. Improvement in symptoms, but not full
Table 1: Characteristics of Patients with Neurologic Impairments.

<table>
<thead>
<tr>
<th>Case/reference Number</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Serum B12 Status</th>
<th>Causes</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [33]</td>
<td>39</td>
<td>Male</td>
<td>• Distal upper extremity numbness • Fine motor difficulties</td>
<td>203 pg/mL</td>
<td>Lack of IF</td>
<td>(B12) Monthly injections</td>
</tr>
<tr>
<td>2 [19]</td>
<td>19</td>
<td>Male</td>
<td>• Painless weakness • Paresthesia • Nummness of palmar aspects of both hands</td>
<td>101 ng/L</td>
<td>Vegetarianism</td>
<td>(B12) IM therapy</td>
</tr>
<tr>
<td>3 [38]</td>
<td>56</td>
<td>Male</td>
<td>• Acute onset of paresthesia involving both hands • Difficulty walking • Inability to feel the ground</td>
<td>75 pg/mL</td>
<td>Lack of IF</td>
<td>Parenteral administration of vitamin B12</td>
</tr>
<tr>
<td>4 [58]</td>
<td>19</td>
<td>Male</td>
<td>• Gradually progressing tingling in both hands</td>
<td>&lt;100 pg/mL</td>
<td>Malabsorption</td>
<td>(B12) Intravenous and IM injections</td>
</tr>
<tr>
<td>5 [20]</td>
<td>39</td>
<td>Male</td>
<td>• Progressive spastic paraparesis</td>
<td>195 ng/L</td>
<td>Vegetarianism</td>
<td>(B12) 1 mg/day for 1 week, weekly for 3 weeks, then every month</td>
</tr>
<tr>
<td>6 [13]</td>
<td>40</td>
<td>Male</td>
<td>• Acute onset of irrelevant speech and inability to comprehend • Involuntary movements of upper extremities • Unsteady gait</td>
<td>62.96 pg/mL</td>
<td>Vegetarianism</td>
<td>Parenteral (B12) 3000 µg/day for 1 month, then 1000 µg/month for 1 month</td>
</tr>
<tr>
<td>7 [18]</td>
<td>68</td>
<td>Male</td>
<td>• Progressive gait instability • Weakness in legs • Paresthesia in feet • Difficulty concentrating</td>
<td>121 pmol/L</td>
<td>Vegetarianism</td>
<td>IM (B12) 1000 µg/day for 1 week, 1/week for 4 weeks, then oral administration</td>
</tr>
<tr>
<td>8 [21]</td>
<td>21</td>
<td>Male</td>
<td>• Burning pain in lower limbs</td>
<td>51 ng/L</td>
<td>Lack of IF</td>
<td>IM (B12) for 1 week, weekly injections for 1 month</td>
</tr>
<tr>
<td>9 [46]</td>
<td>35</td>
<td>Female</td>
<td>• Progressive unsteadiness of gait • Tendency to fall toward the left • Nummness in both legs</td>
<td>100 ng/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg</td>
</tr>
<tr>
<td>10 [31]</td>
<td>35</td>
<td>Male</td>
<td>• Progressive unsteadiness • Slurring of speech • Alteration in mood • Nummness in both legs</td>
<td>&lt;44 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1 mg daily for 1 week, then monthly injections</td>
</tr>
<tr>
<td>11 [47]</td>
<td>37</td>
<td>Female</td>
<td>• Burning pain in lower limbs</td>
<td>51 ng/L</td>
<td>Lack of IF</td>
<td>IM (B12) 5000 µg/week for 1 month than 1000 µg/week</td>
</tr>
<tr>
<td>12 [47]</td>
<td>61</td>
<td>Female</td>
<td>• Fatigue • Cramps • Distal paresthesias in lower legs</td>
<td>53 ng/L</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/day</td>
</tr>
<tr>
<td>13 [32]</td>
<td>38</td>
<td>Female</td>
<td>• Fatigue • Electric dysesthesia with neck flexion (Lhermitte’s sign)</td>
<td>&lt;50 pg/mL</td>
<td>Lack of IF</td>
<td>(B12) 500 µg biweekly</td>
</tr>
<tr>
<td>14 [32]</td>
<td>44</td>
<td>Male</td>
<td>• Fatigue • Nummness in extremities • Intermittent electric dysesthesia associated with neck flexion (Lhermitte’s sign)</td>
<td>42 pg/mL</td>
<td>Lack of IF</td>
<td>B12 therapy</td>
</tr>
<tr>
<td>15 [34]</td>
<td>42</td>
<td>Female</td>
<td>• Nummness and tingling feet • Symmetrical weakness of lower extremities • Urinary incontinence • Sensory loss of perineal region</td>
<td>&lt;150 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/day for 7 days, weekly for 3 weeks, then monthly</td>
</tr>
<tr>
<td>16 [48]</td>
<td>44</td>
<td>Male</td>
<td>• Shortness of breath • Fatigue • Paresthesia</td>
<td>70 ng/L</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/day for 1 week, then weekly for 1 month, then monthly</td>
</tr>
<tr>
<td>17 [53]</td>
<td>44</td>
<td>Male</td>
<td>• Constant tolerable pains in the lumbar area • Nummness in the lower limbs</td>
<td>75 pmol/L</td>
<td>Lack of IF</td>
<td>(B12) 1000 g for 30 days, then 500 g for 15 days</td>
</tr>
<tr>
<td>18 [36]</td>
<td>55</td>
<td>Male</td>
<td>• Bradykinesia • Tremors of hands</td>
<td>5 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 mg/day for 3 days then 1/week for 4 weeks</td>
</tr>
<tr>
<td>19 [37]</td>
<td>55</td>
<td>Male</td>
<td>• Weakness and nummness in extremities • Difficulty walking • Deterioration of mental activities</td>
<td>&lt;30 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/day for 7 days, then 1000 µg/week</td>
</tr>
<tr>
<td>Case/reference Number</td>
<td>Age</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Serum B12 Status</td>
<td>Causes</td>
<td>Treatment</td>
</tr>
<tr>
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</tr>
<tr>
<td>20 [49]</td>
<td>57 years Male</td>
<td>• Difficulty in walking</td>
<td>146 ng/L</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/day for 3 weeks, monthly for 6 months, then 100 µg oral/daily</td>
<td></td>
</tr>
<tr>
<td>21 [55]</td>
<td>62 years Male</td>
<td>• Choreatic movements in upper arms and head</td>
<td>104 pmol/L</td>
<td>Lack of IF</td>
<td>IM (B12) 1mg/day for 10 days, then weekly</td>
<td></td>
</tr>
<tr>
<td>22 [50]</td>
<td>66 years Female</td>
<td>• Ataxia of stance and gait</td>
<td>338 ng/L</td>
<td>Lack of IF</td>
<td>(B12) 1 mg/day for 12 days, then 1/week</td>
<td></td>
</tr>
<tr>
<td>23 [51]</td>
<td>70 years Female</td>
<td>• History of imbalance</td>
<td>247 pg/mL</td>
<td>Unknown</td>
<td>IM (B12) 1mg/day for 5 days, then monthly</td>
<td></td>
</tr>
<tr>
<td>24 [51]</td>
<td>74 years Female</td>
<td>• Gait disturbance</td>
<td>86 ng/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1 mg/day for 10 days, then monthly</td>
<td></td>
</tr>
<tr>
<td>25 [41]</td>
<td>77 years Male</td>
<td>• Unstable gait</td>
<td>38 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1mg/day for 1 week then 1 mg/month</td>
<td></td>
</tr>
<tr>
<td>26 [42]</td>
<td>78 years Male</td>
<td>• Weakness in the left arm and shoulder</td>
<td>116 pg/mL</td>
<td>Lack of IF</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>27 [45]</td>
<td>55 years Male</td>
<td>• Paresthesias</td>
<td>142 pg/mL</td>
<td>Unknown</td>
<td>Parenteral (B12) 1000 µg/month</td>
<td></td>
</tr>
<tr>
<td>28 [45]</td>
<td>87 years Male</td>
<td>• Progressively weakening gait</td>
<td>&lt;100 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/month</td>
<td></td>
</tr>
<tr>
<td>29 [64]</td>
<td>28 years Male</td>
<td>• Lethargy</td>
<td>1365 pmol/L</td>
<td>Malabsorption</td>
<td>IM (B12) 1 mg weekly</td>
<td></td>
</tr>
<tr>
<td>30 [62]</td>
<td>35 years Male</td>
<td>• Progressive weakness of lower limbs</td>
<td>121 ng/L</td>
<td>Malabsorption</td>
<td>IM (B12) 1000 µg/day for 2 weeks, weekly for 2 months, then monthly</td>
<td></td>
</tr>
<tr>
<td>31 [63]</td>
<td>73 years Female</td>
<td>• Progressive gait deterioration</td>
<td>349 ng/L</td>
<td>Malabsorption</td>
<td>IM (B12) 3 monthly injections</td>
<td></td>
</tr>
<tr>
<td>32 [65]</td>
<td>57 years Male</td>
<td>• Clumsiness</td>
<td>135 pmol/L</td>
<td>Nitrous oxide exposure</td>
<td>IM (B12) 1000 µg/day for five days</td>
<td></td>
</tr>
<tr>
<td>33 [65]</td>
<td>52 years Male</td>
<td>• Paresthesia of feet, trunk, chest, and arms</td>
<td>166 pmol/L</td>
<td>Nitrous oxide exposure</td>
<td>IM (B12) 5000 µg/day for five days</td>
<td></td>
</tr>
<tr>
<td>34 [66]</td>
<td>65 years Male</td>
<td>• Problems walking</td>
<td>&lt;30 µg/L</td>
<td>Nitrous oxide exposure</td>
<td>Replacement B12 therapy</td>
<td></td>
</tr>
<tr>
<td>35 [67]</td>
<td>20’s Female</td>
<td>• Increasing difficulty in mobilizing</td>
<td>124 pmol/L</td>
<td>Nitrous oxide exposure</td>
<td>B12 replacement therapy</td>
<td></td>
</tr>
<tr>
<td>36 [68]</td>
<td>23 years Female</td>
<td>• Profound tetraparesis</td>
<td>125 pmol/L</td>
<td>Nitrous oxide exposure</td>
<td>(B12) 5000 µg/day for 12 days</td>
<td></td>
</tr>
<tr>
<td>37 [70]</td>
<td>60 years Male</td>
<td>• Behavior changes</td>
<td>60 pg/mL</td>
<td>Metformin therapy</td>
<td>IM (B12) once a week for 4 weeks</td>
<td></td>
</tr>
<tr>
<td>38 [72]</td>
<td>82 years Female</td>
<td>• Memory loss</td>
<td>97 pmol/L</td>
<td>Metformin therapy</td>
<td>(B12) 1000 µg on alternate days for 5 days followed by 1000 µg monthly</td>
<td></td>
</tr>
<tr>
<td>39 [73]</td>
<td>69 years Male</td>
<td>• Numbness in feet</td>
<td>Not reported</td>
<td>Metformin therapy</td>
<td>IM B12 therapy</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2: Characteristics of Patients with Psychiatric Abnormalities.

<table>
<thead>
<tr>
<th>Case/reference Number</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Serum B12 Status</th>
<th>Causes</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [61]</td>
<td>65 years</td>
<td>Male</td>
<td>Persecutory delusions</td>
<td>110 pg/mL</td>
<td>Malabsorption</td>
<td>(B12) Daily intramuscular at 1000 µg/d</td>
</tr>
<tr>
<td>2 [39]</td>
<td>64 years</td>
<td>Male</td>
<td>Confusion, Collapse, Deterioration of work efficiency</td>
<td>307 pg/mL</td>
<td>Lack of IF</td>
<td>Substitution of vitamin B12</td>
</tr>
<tr>
<td>3 [39]</td>
<td>77 years</td>
<td>Male</td>
<td>Delusional fear of impoverishment, Disoriented, Depressed mood</td>
<td>203 pg/mL</td>
<td>Lack of IF</td>
<td>Vitamin B12</td>
</tr>
<tr>
<td>4 [43]</td>
<td>81 years</td>
<td>Male</td>
<td>Irritable mood, Hyperactivity, Decreased need for sleep, Gradiosity, Sexual indiscretion, Reckless and agitated behavior</td>
<td>116 pg/mL</td>
<td>Lack of IF</td>
<td>(B12) 1000 µg i.v., for 1 week, then with weekly injections at the same dose.</td>
</tr>
<tr>
<td>5 [11]</td>
<td>27 years</td>
<td>Male</td>
<td>Forgetfulness, Social withdrawal, Paucity of speech, Decreased interest, Apathy</td>
<td>&lt;50 pg/mL</td>
<td>Vegetarianism</td>
<td>IM (B12) injections</td>
</tr>
<tr>
<td>6 [12]</td>
<td>33 years</td>
<td>Female</td>
<td>Sad mood, Fatigue, Lack of interest, Sleep disturbances, Weight loss</td>
<td>82 pg/mL</td>
<td>Vegetarianism</td>
<td>IM (B12) 1000 ng/day for 10 days</td>
</tr>
<tr>
<td>7 [14]</td>
<td>52 years</td>
<td>Female</td>
<td>Catatonia, Mute, Odd motor movements, Wavy flexibility, Active negativism, Perplexed look, Incontinence</td>
<td>150 pg/mL</td>
<td>Vegetarianism</td>
<td>IM (B12) 1000 µg on alternating days for 3 days plus an oral tablet daily. Followed by weekly IM (B12)</td>
</tr>
<tr>
<td>8 [25]</td>
<td>66 years</td>
<td>Female</td>
<td>Sad mood, Lack of energy, interest, and motivation, Sleep disturbances</td>
<td>&lt;100 pg/mL</td>
<td>Malnutrition</td>
<td>Series of IM (B12) injections</td>
</tr>
<tr>
<td>9 [22]</td>
<td>67 years</td>
<td>Female</td>
<td>Irrational behavior, Tremor in hand, Deteriorating handwriting, Forgetfulness</td>
<td>79 pmol/L</td>
<td>Malnutrition</td>
<td>IM (B12) 1000 µg/day</td>
</tr>
<tr>
<td>10 [40]</td>
<td>72 years</td>
<td>Male</td>
<td>Apathy, Irritability, Deterioration of attention and memory, Psychotic episodes, Paranoid thoughts, Jealous delusions</td>
<td>54 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg 3x/week for 45 days, weekly for 45 days, then monthly</td>
</tr>
<tr>
<td>11 [59]</td>
<td>23 years</td>
<td>Female</td>
<td>Distress, Catatonic, Mute, Paranoid</td>
<td>&lt;100 pg/mL</td>
<td>Malabsorption</td>
<td>Aggressive B12 supplementation</td>
</tr>
</tbody>
</table>
### Case/reference Number | Age | Sex | Symptoms | Serum B12 Status | Causes | Treatment |
--- | --- | --- | --- | --- | --- | --- |
12 [60] | 64 years | Male | • Depressed mood  • Anhedonia and loss of interest  • Loss of appetite and weight loss  • Difficulty with falling asleep and concentrating  • Fatigue  • Delusions | 169 pg/mL | Malabsorption | IM (B12) 1000 µg/day for 2 weeks then weekly for 2 weeks, then continuous treatment |
13 [69] | 33 years | Female | • Bizarre behavior  • Delusions | 202 pg/mL | Nitrous oxide exposure | IM (B12) 1000 µg every day for one week, then every month for one month |
14 [74] | 31 years | Male | • Insomnia  • Suspiciousness  • Hearing voices  • Social withdrawal  • Functional impairment | 201 pg/mL | Unknown | IM (B12) daily for 1 week, then once a week for 4 weeks |
15 [77] | 35 years | Female | • Manic symptoms  • Gradiosity  • Hyperactivity  • Sexual indiscretion  • Hyperphagia  • Irritable mood  • Reckless behavior  • Flight of ideas  • Overbearing manner | 60 pg/mL | Unknown | IM (B12) 1000 µg/day for a week, weekly for one month, then monthly |
16 [82] | 78 years | Female | • Visual hallucinations | 44 pmol/L | Unknown | Oral vitamin (B12) 1mg daily |

### Table 3: Characteristics of Patients with Oral Manifestations.

| Case/reference Number | Age | Sex | Symptoms | Serum B12 Status | Causes | Treatment |
--- | --- | --- | --- | --- | --- | --- |
1 [23] | 73 years | Male | • Pain and burning sensation in tongue  • Increased sensitivity to tongue’s sensations (post chemical exposure) | 140 pmol/L | Malnutrition | (B12) Individual injectable IM administration |
2 [56] | 54 years | Female | • Stomatitis  • Glossitis | <44 pmol/L | Unknown | (B12) 1 mg/day IM for 5 days, followed by 1 mg monthly |
3 [56] | 36 years | Male | • Migratory glossitis | <44 pmol/L | Unknown | (B12) 1 mg/day IM for 5 days, followed by 1 mg monthly |
4 [56] | 33 years | Female | • Acute glossitis | <44 pmol/L | Unknown | (B12) 1 mg/day IM for 5 days, followed by 1 mg monthly |
5 [56] | 68 years | Female | • Glossitis | 25 pmol/L | Unknown | (B12) 1 mg/day IM for 5 days, followed by 1 mg monthly |
6 [8] | 61 years | Male | • Gradually progressive hoarseness  • Vocal fold palsy | Not reported | Excessive alcohol consumption | (B12) IM administration |
7 [16] | 41 years | Female | • Difficulty in eating foods (banana/tomato) because of burning sensation  • Presence of red stains on inside of cheeks and tongue | Not reported | Vegetarianism | Monthly injections of vitamin B12 replacement therapy |
8 [15] | 30 years | Female | • Recurrent aphthous stomatitis (canker sores) | 65.1 pmol/L | Semi-vegetarianism | (B12) 1000 µg parenteral 2x/week for 6 weeks followed by injections 1x/month for 1 year |
9 [15] | 28 years | Male | • Recurrent aphthous stomatitis (canker sores) | 124.5 pmol/L | Semi-vegetarianism | (B12) 1000 µg parenteral 2x/week for 6 weeks followed by injections 1x/month for 1 year |
10 [15] | 19 years | Female | • Recurrent aphthous stomatitis (canker sores) | 64.2 pmol/L | Unknown | (B12) 1000 µg parenteral 2x/week for 6 weeks followed by injections 1x/month for 1 year |
11 [30] | 31 years | Female | • Recurrent aphthous stomatitis (canker sores) | < 50 pg/mL | Lack of IF | IM (B12) 1000 µg/day for 1 week, followed by once every two weeks |
12 [52] | 73 years | Female | • Sore, burning tongue  • Increased tongue sensitivity | 144 mg/L | Lack of IF | Oral B12 100 µg/day |
13 [83] | 88 years | Female | • Tongue and mouth discomfort  • Oral epithelial dysplasia | 60 mg/L | Unknown | IM (B12) 1 mg every 3 days |

Rusher and Pawlak (2013)
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remission was observed in 39 cases. Five cases indicated little to no improvement in symptoms, \[42,51,53,63,73\] and three cases did not report a treatment outcome \[27,30,43\].

**BIOMARKERS OF B12 STATUS**

Biomarkers of B12 status reported in the cases included serum B12 levels, mean corpuscular volume (MCV), and serum homocysteine. Serum methylmalonic acid (MMA) is an additional biomarker of B12 status; however, it was not widely reported in the cases reviewed. Serum B12 level was reported in all but two cases \[8,16\]. MCV levels were reported in 53 cases and serum homocysteine levels in 13 cases.

A notable case to report was of a 40 years of age male patient who initially had normal B12 level, however, he demonstrated progressive neurological symptoms and repeat MR imaging indicated posterior cervical cord lesions. A second test of B12 levels indicated a low B12 status of 41 pg/mL. The authors recommend that in cases where B12 is in the low normal range at first test, levels of methylmalonic acid and homocysteine should

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**Table 4: Characteristics of Patients with Dermatological Manifestations.**

<table>
<thead>
<tr>
<th>Case/reference Number</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Serum B12 Status</th>
<th>Causes</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [10]</td>
<td>25</td>
<td>Female</td>
<td>Blackish discoloration of the skin on knuckles</td>
<td>31.6 pg/mL</td>
<td>Vegetarianism</td>
<td>Oral B12 replacement</td>
</tr>
<tr>
<td>2 [17]</td>
<td>34</td>
<td>Female</td>
<td>Skin lesions on feet</td>
<td>113 pmol/L</td>
<td>Unknown</td>
<td>IM (B12) 1000 µg/day</td>
</tr>
<tr>
<td>3 [17]</td>
<td>54</td>
<td>Female</td>
<td>Skin lesions on neck and upper and lower limbs</td>
<td>100 pmol/L</td>
<td>Vegetarianism</td>
<td>IM (B12) 1000 µg/day</td>
</tr>
<tr>
<td>4 [24]</td>
<td>54</td>
<td>Male</td>
<td>Darkening of hands, feet, and tongue (hyperpigmentation)</td>
<td>35 pg/mL</td>
<td>Malnutrition</td>
<td>IM (B12) 1 mg every week for 2 months, then every month for 3 months</td>
</tr>
<tr>
<td>5 [35]</td>
<td>43</td>
<td>Male</td>
<td>Increased skin pigmentation</td>
<td>34.34 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 100 mg/day for 7 days, then 2x/week for 3 weeks, then 100 mg once a month</td>
</tr>
</tbody>
</table>

**Table 5: Characteristics of Patients with Rare Manifestations.**

<table>
<thead>
<tr>
<th>Case/reference Number</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Serum B12 Status</th>
<th>Causes</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [9]</td>
<td>18</td>
<td>Male</td>
<td>Fatigue, High-grade pyrexia (fever)</td>
<td>105 pg/mL</td>
<td>Vegetarianism</td>
<td>(B12) 1000 mcg/day IM</td>
</tr>
<tr>
<td>2 [26]</td>
<td>26</td>
<td>Female</td>
<td>Gradual and painless visual loss</td>
<td>54 ng/L</td>
<td>Malnutrition (poor diet)</td>
<td>B12 supplementation</td>
</tr>
<tr>
<td>3 [27]</td>
<td>22</td>
<td>Female</td>
<td>Malaise, Anorexia, Exercise intolerance</td>
<td>52 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 100 µg/day for 10 days, followed by monthly injections</td>
</tr>
<tr>
<td>4 [28]</td>
<td>24</td>
<td>Male</td>
<td>Persistent watery diarrhea, Anorexia, Weight loss</td>
<td>110 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) monthly</td>
</tr>
<tr>
<td>5 [29]</td>
<td>26</td>
<td>Male</td>
<td>Complex partial seizures, Social withdrawal, Memory impairment</td>
<td>26 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) injections</td>
</tr>
<tr>
<td>6 [54]</td>
<td>52</td>
<td>Male</td>
<td>Shortness of breath, General weakness, Weight loss, Sore tongue, Pancytopenia</td>
<td>52 pmol/L</td>
<td>Lack of IF</td>
<td>IM (B12) for 7 days, then weekly for 4 weeks, then once a month</td>
</tr>
<tr>
<td>7 [44]</td>
<td>85</td>
<td>Female</td>
<td>Intermittent, brief, painless involuntary movements in the abdominal muscles</td>
<td>&lt;90 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/day for 7 days, then 1000 µg/week</td>
</tr>
<tr>
<td>8 [57]</td>
<td>18</td>
<td>Male</td>
<td>Short stature, Prepubertal sexual maturation, Exertional dyspnea</td>
<td>60 pg/mL</td>
<td>Malabsorption</td>
<td>IM (B12) 100 µg/day for 14 days, then 50 µg every other week</td>
</tr>
<tr>
<td>9 [81]</td>
<td>59</td>
<td>Male</td>
<td>Collapse to unconsciousness, Generalized tonic-clonic seizure activity, Mild headaches, Occasional diaphoresis</td>
<td>90 pmol/L</td>
<td>Unknown</td>
<td>IM (B12) replacement therapy</td>
</tr>
<tr>
<td>10 [80]</td>
<td>80</td>
<td>Male</td>
<td>Extreme fatigue, Fainting, Jaundice, Headache, Vertigo, Insomnia, Nocturnal dyspnea</td>
<td>129 pg/mL</td>
<td>Unknown</td>
<td>IM (B12) 1 mg/day for 25 days, 1 mg/week for 8 weeks, then monthly</td>
</tr>
</tbody>
</table>
DISCUSSION

B12 deficiency can occur due to a number of causes and can affect people of various ages and backgrounds. As formerly noted, the causes of B12 deficiency can be grouped into four main categories including, nutritional B12 deficiency, lack of IF or malabsorption of protein-bound B12, general malabsorption, and competition for B12.

As already mentioned, B12 is naturally present only in meats and foods of animal origin. Therefore, individuals that do not eat any animal products, such as vegans, are at high risk for deficiency if they do not consume adequate amounts of fortified products or supplements. A total of 13 cases reported deficiency due to vegetarians [9-20]. Of these, six were vegetarian (1 lacto-vegetarian), [11,12,14,17-19] five were vegan, [9,10,13,16,20] and two were semi-vegetarian [15]. Three cases reported diet durations for the patients. These cases included one life-long vegan, [9] one life-long vegetarian, [11] and one vegan who had followed the diet for 2.5 years [16]. Previous studies have shown that compared to omnivores and vegetarians, vegans have a lower average serum concentration of B12 [4]. Some studies have also suggested that compared to omnivores, vegetarians have lower B12 serum concentrations [4]. One review indicated that vegetarians develop deficiency regardless of the type of diet, geographical location where they reside, or any other factors [84]. As such, it is imperative that those who follow a vegetarian or vegan diet consume adequate amounts of B12 fortified food products and/or take supplements containing B12 to prevent deficiency.

Lack of IF is the most common cause of impaired vitamin B12 absorption, which can be seen in patients who suffer from gastric atrophy [17]. Malabsorption of protein-bound vitamin B12 is often observed in the elderly population where gastric acid is not produced in sufficient amounts to proteolyze B12 from proteins [17]. This is often the result of atrophic gastritis where the fundus glands and parietal cell mass are reduced [17]. A total of 36 cases reported B12 deficiency due to lack of IF or malabsorption of protein-bound B12. This represented the most common cause of deficiency among the cases reviewed. Although lack of IF, as mentioned is commonly observed in the elderly population, it is not exclusive to this population. Of the cases reviewed, the majority (22 cases) represented patients below the age of 65. Moreover, it appears that lack of IF could be a prominent cause of B12 deficiency among young and middle-aged adults. The Dietary Guidelines for Americans currently recommends that individuals aged 50 years and older should take a B12 supplement [85]. The findings of the cases reviewed indicate that this recommendation may have to be extended to individuals in younger age groups.

General malabsorption leading to B12 deficiency can be encountered among individuals having undergone bowel resection especially at the terminal ileum. This is because the terminal ileum is the site of B12 absorption [2]. Three cases presented B12 deficiency due to bowel resection. One case involved small bowel resection, [57] one involved resection due to congenital necrotizing ileus, [59] and one had a resection of the terminal ileum due to DLBCL [60]. Individuals having undergone bowel resection should be screened for B12 deficiency at regular intervals. Moreover, a prudent measure would be for these patients to receive regular B12 injections, as the use of supplements may not be effective in correcting deficiency due to their malabsorptive state.

Competition for vitamin B12 leading to deficiency can occur with use of some medications [17]. One of these medications is nitrous oxide. Nitrous oxide irreversibly oxidizes the cobalt ion of B12 and therefore inactivates it [68]. Nitrous oxide, or “laughing gas” is often used as an analgesic before short medical procedures to elevate mood. [68] Three cases were reviewed which presented post-operative occurrences of B12 deficiency as a result of nitrous oxide exposure during surgery [65,66]. Nitrous oxide is also misused recreationally by inhalation of the gas from whipped cream dispensers. Three reports presented cases of nitrous oxide induced vitamin B12 deficiency as a result of recreational misuse [67-69]. B12 deficiency resulting from nitrous oxide exposure is well documented and can result in subacute combined degeneration (SCD) of the spinal cord [65]. SCD of the spinal cord involves degeneration of the posterior and lateral columns [67]. Of the cases involving B12 deficiency due to nitrous oxide exposure, five reported SCD as a resulting complication [65-69]. Individuals having undergone surgery where nitrous oxide was used as an analgesic should be made aware of the potential effect this has on B12 status. Additionally, they should be screened post-operatively for indicators of B12 deficiency. Physicians should also be made aware of the detrimental effects associated with the recreational misuse of nitrous oxide in regards to B12 deficiency, so they will be able to treat patients quickly and appropriately.

Metformin for the treatment of diabetes is another medication that when used can lead to B12 deficiency. Although the responsible mechanism for metformin inducing B12 deficiency is controversial it is proposed that metformin affects the calcium-dependent ileal cell membrane receptors needed for B12-intrinsic factor uptake [72]. Metformin-induced vitamin B12 deficiency was indicated in five cases [70-73]. Metformin is the leading anti-diabetic drug sold in the US with more than 30 million generic prescriptions distributed to patients in 2009 [86]. Approximately 30% of patients undergoing metformin therapy experience B12 malabsorption [86]. It is indicated that metformin reduces the absorption of B12 by up to 30% and reduces serum B12 concentrations by 5-10% [86]. Moreover, B12 deficiency may exacerbate many diabetes co-morbidities such as poor circulation and neuropathy. Thus it is imperative that screening for B12 deficiency occurs among patients undergoing metformin therapy.

The clinical manifestations of B12 deficiency are varied and include neurological, psychiatric, oral, and dermatological signs and symptoms. A total of 43 cases involved neurological complications as a result of B12 deficiency. The main features of neurological impairment observed in the cases reviewed included paresthesia (27 cases), ataxia (22 cases), and weakness (13 cases) of the extremities. Psychiatric abnormalities were observed in 16 cases. The main features of psychiatric manifestations observed included delusions (5 cases), irritability (5 cases), decreased interest (5 cases), and sleep disturbances (4 cases). Oral manifestations were reported in 13 cases, and included symptoms...
such as glossitis (4 cases), recurrent aphthous stomatitis (4 cases), and pain and burning sensations in the mouth (4 cases). Dermatological symptoms were indicated in five cases and the most prevalent manifestation was hyperpigmentation (3 cases).

Clinical manifestations of B12 deficiency were observed in nine cases where serum B12 levels were higher than what is commonly accepted as a deficiency [33,39,50,51,63,64,69,74]. Six of these cases reported serum B12 levels from 201-307 pg/mL, [33,39,51,69,74] two indicated levels of 338 and 349 ng/mL [50,63] and one case reported a very high serum B12 level of 1365 pmol/L [64]. Further investigation of this patient with functional B12 deficiency indicated that although serum B12 levels were high, the patient had a very low red blood cell vitamin B12 level and high levels of homocysteine and MMA. The findings of these cases confirm that serum B12 levels may not be the most reliable method for assessment of B12 status and that other biomarkers of B12 status should be utilized in concurrence with serum B12 levels to make an accurate diagnosis. Studies have indicated that serum or plasma B12 and MCV can be unreliable methods for the assessment of B12 levels [87]. Transcobalamin II (TCII) and MMA are currently considered the most precise assessment methods [87].

There are various methods of B12 replacement therapy included parenteral (or intravenous) replacement, intramuscular (IM) therapy, or oral B12 replacement. The vast majority of cases (59 cases) reviewed used the IM method to restore serum B12 levels, with many cases utilizing a dose of 1000 µg in a staggered therapeutic approach. Forty cases reported complete remission of deficiency symptoms with B12 therapy, while 39 cases reported improvement. This highlights the need for emphasis on the prevention of B12 deficiency as many of the symptoms, especially neurological, did not reverse completely with B12 replacement therapy. All but one patient [52] experiencing oral manifestations of B12 deficiency experienced complete resolution of symptoms (one case was unreported) [30]. Similarly, all but one case experiencing dermatological symptoms indicated full recovery [17]. This indicates that B12 deficiency manifesting as oral or dermatological symptoms may be relatively easy to treat. Moreover, the five cases which reported little to no improvement in symptoms were all neurological, and may indicate that these symptoms are resistant to treatment and in some instances may not be reversible [42,51,53,63,73]. In these cases, prevention may be the best medicine.

B12 deficiency can be prevented by adequate intake of B12 containing food products such as meat, fish, eggs, and dairy products; [3] or B12 containing fortified plant products such as cereals, plant-based milks, soy products, and B12-fortified yeast extract. However, meat and animal products are often recommended to be limited due to either prevention or management of chronic health conditions, while fortified foods usually contain small doses of this vitamin. If dietary adequacy is a probable cause, B12 containing supplements should be considered. Another method to prevent deficiency that has been proposed is the fortification of flour with B12 [87]. In order to be effective among groups at a high risk for deficiency the flour would likely have to be fortified at a dose of 100 µg or greater per 100 g [87]. Keller et al. suggested a novel way of preventing B12 deficiency using B12-fortified tooth paste [88]. In their study with vegans and vegetarians with low B12 status all biomarkers measured including TCII, total homocysteine and serum B12 values were normalized after 5 weeks duration of the experiment. Unfortunately, they did not report the dose of fortification of the toothpaste.

Biomarkers of B12 status include serum B12 level, MCV, serum homocysteine, and MMA. Serum B12 levels were overwhelmingly utilized as the indicator of B12 status having been utilized in all but two cases. MCV levels were reported in 53 cases and homocysteine in 13 cases. To achieve more reliable B12 status, clinicians should consider utilizing two different assessment methods, especially MMA and TCII.

REFERENCES


