Vitamin B\textsubscript{12} deficiency is common among the elderly. Elderly people are particularly at risk of vitamin B\textsubscript{12} deficiency because of the high prevalence of atrophic gastritis–associated food-cobalamin (vitamin B\textsubscript{12}) malabsorption, and the increasing prevalence of pernicious anaemia with advancing age. The deficiency most often goes unrecognised because the clinical manifestations are highly variable, often subtle and non-specific, but if left undiagnosed the consequences can be serious. Diagnosis of vitamin B\textsubscript{12} deficiency, however, is not straightforward as laboratory tests have certain limitations. Setting a cut-off level to define serum vitamin B\textsubscript{12} deficiency is difficult; though homocysteine and methylmalonic acid are more sensitive for vitamin B\textsubscript{12} deficiency, it may give false result in some conditions and the reference intervals are not standardised. At present, there is no consensus or guideline for diagnosis of this deficiency. It is most often based on the clinical symptoms together with laboratory assessment (low serum vitamin B\textsubscript{12} level and elevated serum homocysteine or methylmalonic acid level) and the response to treatment to make definitive diagnosis. Treatment and replacement with oral vitamin B\textsubscript{12} can be as effective as parenteral administration even in patients with pernicious anaemia. The suggested oral vitamin B\textsubscript{12} dose is 1 mg daily for a month, and then maintenance dose of 125 to 250 μg for patients with dietary insufficiency and 1 mg daily for those with pernicious anaemia. Vitamin B\textsubscript{12} replacement is safe and without side-effects, but prompt treatment is required to reverse the damage before it becomes extensive or irreversible. At present, there is no recommendation for mass screening for vitamin B\textsubscript{12} in the elderly. Nevertheless, the higher prevalence with age, increasing risk of vitamin B\textsubscript{12} deficiency in the elderly, symptoms being difficult to recognise, and availability of safe treatment options make screening a favourable option. However, the unavailability of reliable diagnostic tool or gold standard test makes screening difficult to carry out.
老年人的維生素B₁₂缺乏症：是否值得篩檢？

王哲慧

老年人中有維生素B₁₂缺乏症的情況相當普遍。由於老年人經常患有萎縮性胃炎，以致未能從食物中吸收足夠的钴胺素（即維生素B₁₂），加上年紀愈大愈容易患上惡性貧血，因此老年人出現維生素B₁₂缺乏的風險較高。這種缺乏症的病徵並不明顯，臨床表現高度變異，診斷維生素B₁₂缺乏症的難度很大。診斷維生素B₁₂缺乏症的實驗室評估標準是低於150 pmol/L的血清維生素B₁₂水平，或有增高的趨勢，加上年紀愈大愈容易患有惡性貧血病，因此老年人出現維生素B₁₂缺乏的風險較高。目前已有安全的治療方案，這一切都顯示維生素B₁₂不可逆轉的境況前，應及早治療。目前尚未有對老年人作維生素B₁₂缺乏症的篩檢方案。然而，由於此症的發病率會隨著年齡增長而有增高的趨勢，加上年紀愈大愈容易對治療的反應差，所以維生素B₁₂缺乏症的篩檢方案缺乏。老年人中有維生素B₁₂缺乏症的情況相當普遍。因此，建議制定適當的維生素B₁₂缺乏症的篩檢方案，以減少此症的後果。

### Diagnosis of vitamin B₁₂ deficiency

There is no precise or ‘gold standard’ test to diagnose vitamin B₁₂ deficiency. The diagnosis is usually based on identifying a low level of serum vitamin B₁₂ with clinical evidence of deficiency, which responds to vitamin B₁₂ replacement therapy. When there is a clinical suspicion of vitamin B₁₂ deficiency, the initial laboratory assessment includes serum vitamin B₁₂ levels, complete blood count, and blood film examination. Although the blood picture and classical finding of vitamin B₁₂ is megaloblastic anaemia, often times this is not seen especially in mild cases of vitamin B₁₂ deficiency. The investigations for vitamin B₁₂ deficiency are traditionally recommended for patients with macrocytosis, but macrocytosis with or without anaemia is neither specific nor sensitive to confirm the diagnosis. The reason for this is that macrocytosis can also be found in other conditions like folate deficiency and myelodysplastic disorders, and up to 84% of cases would be missed if macrocytosis is used as the only parameter to screen for vitamin B₁₂ deficiency.

Tests to measure and quantify serum vitamin B₁₂ levels in the body are readily available and inexpensive. However, the screening test has some limitations and drawbacks. The main drawback is that there is no universally accepted serum vitamin B₁₂ cut-off to define deficiency although the value of <150 pmol/L (200 pg/mL) is often used, and at this serum vitamin B₁₂ level or below, metabolites like serum homocysteine, serum and urine MMA, become elevated. The World Health Organization has suggested to use this cut-off to define vitamin B₁₂ deficiency since the year 2008. However, some have argued that the cut-off value of 150 pmol/L is too low and inevitably does not reflect a sufficient level of vitamin B₁₂ in the body, and more so the clinical symptoms of vitamin B₁₂ deficiency like neurological symptoms can occur even if serum vitamin B₁₂ is above 150 pmol/L. Thus, a higher cut-off value of 220 to 258 pmol/L (298-350 pg/mL) based on more sensitive indicators of vitamin B₁₂ status like elevated serum homocysteine, serum and urine MMA, become elevated. The World Health Organization has suggested to use this cut-off to define vitamin B₁₂ deficiency since the year 2008.

### B₁₂ cut-off alone

The prevalence of vitamin B₁₂ deficiency is estimated to be in the range of 5% to 15%. However, when higher serum vitamin B₁₂ cut-off at 258 pmol/L (350 pg/mL) or using elevated serum homocysteine or MMA level in addition to a low or low-to-normal serum vitamin B₁₂ level to diagnose vitamin B₁₂ deficiency, the prevalence of deficiency increases to 40.5%. Also, the prevalence of vitamin B₁₂ deficiency appears to increase with age among the elderly population. Furthermore, reports have indicated that institutionalised elderly with multiple co-morbidities and with increasing dependency are more prone to vitamin B₁₂ deficiency than non-institutionalised (free-living) elderly. In such individuals, the prevalence of vitamin B₁₂ deficiency has been reported to reach 30% to 40%.

In our unpublished study on 2096 institutionalised elderly residents aged >65 years, the prevalence of serum vitamin B₁₂ level of <150 pmol/L was 34.9%, whilst in another local study conducted on non-institutionalised (free-living) elderly residents aged over 70 years, the prevalence of vitamin B₁₂ level of <140 pmol/L was only 6.6%.

### Vitamin B₁₂ deficiency

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FIG 1. Sites of vitamin B₁₂ absorption and causes of deficiency

Abbreviations: B = vitamin B₁₂; HCl = hydrochloric acid; I = intrinsic factor; P = animal protein; PPI = proton pump inhibitor; R = protein; TC = transcobalamin

Adapted from Reference 29, with permission from Prof E Andrès
vitamin B₁₂ deficiency. There is compensatory elevation of homocysteine and MMA levels preceding the drop in serum vitamin B₁₂ level and these are regarded as more sensitive indicators of vitamin B₁₂ deficiency than just low serum vitamin B₁₂ level.¹¹,¹²,¹⁶,¹⁷ Elevated serum homocysteine and MMA level (>3 standard deviations above the mean in normal subjects) has a sensitivity of 95.9% and 98.4%, respectively to diagnose vitamin B₁₂ deficiency.¹⁶ However, the reference intervals for serum MMA and homocysteine are variable among different laboratories. Serum MMA of 100 to 750 nmol/L, urine MMA of 1 to 4 nmol/L, and serum homocysteine of 6 to 29 μmol/L are the reference ranges for most methods.¹⁰ If the normalisation of elevated serum homocysteine and MMA levels in response to vitamin B₁₂ replacement therapy is used as a diagnosis of deficiency, up to 50% of patients may be missed when the diagnosis is based on low vitamin B₁₂ level (150 pmol/L) alone.¹⁸,¹⁹ Rise in homocysteine level before increase in MMA is an early indicator of vitamin B₁₂ deficiency. However, this is less specific than elevated MMA level for vitamin B₁₂ deficiency, since such elevated homocysteine levels can occur even in vitamin B₁₂ and folate deficiency states. Both homocysteine and MMA levels can be elevated in renal insufficiency, hypovolaemia, and inherited metabolic defects.¹¹ Although elevated homocysteine and MMA levels can aid in the diagnosis of vitamin B₁₂ deficiency in people with ‘normal’ serum vitamin B₁₂ levels, there are concerns about these metabolite assays. Some have reported that serum MMA and homocysteine levels increase with age and the prevalence of elevated MMA and homocysteine levels is higher than the prevalence of low vitamin B₁₂ or clinically evident vitamin B₁₂ deficiency in the elderly.¹⁰,¹¹,¹⁶,¹⁷ In this regard, using the assay for metabolites alone may result in overdiagnosis and overtreatment. The rationale for these findings is uncertain and some have suggested that it may be related to the increased prevalence of subclinical vitamin B₁₂ deficiency in the elderly. Moreover, these add to the controversies about whether to use metabolite estimation as the initial test to diagnose vitamin B₁₂ deficiency. Besides, other important considerations are that they are more expensive, not readily available, and reference intervals are not standardised. Currently, the initial test for vitamin B₁₂ deficiency is to assess serum vitamin B₁₂ levels, and only when there is low normal vitamin B₁₂ level, metabolite assay is most often suggested.¹¹,¹² However, the consensus for vitamin B₁₂ threshold levels for ordering the additional tests has not yet been reached.

In addition to elevation in homocysteine and MMA levels, a decrease in serum holotranscobalamin level is also considered an early marker for vitamin B₁₂ deficiency. Holotranscobalamin is composed of vitamin B₁₂ attached to a transport protein, transcobalamin II. It is a biologically active fraction of vitamin B₁₂ that can be readily taken up by all cells and represents only 6% to 20% of total serum vitamin B₁₂.²¹ In vitamin B₁₂ deficiency, serum level of holotranscobalamin decreases even before elevation in homocysteine and MMA levels occurs.²¹ It has been shown that holotranscobalamin is the most sensitive marker for vitamin B₁₂ deficiency, followed by MMA.²³,²⁵ Like homocysteine and MMA, holotranscobalamin cannot be tested in renal patients as its level increases in renal impairment.²³ Furthermore, higher cost and lesser availability than homocysteine and MMA testing make it difficult to acquire wide clinical acceptance.

**Causes of vitamin B₁₂ deficiency in the elderly**

As we know elderly people are particularly at risk of vitamin B₁₂ deficiency. The main aetiologies can be divided under two main categories: inadequate dietary intake and impaired absorption of vitamin B₁₂ (Table 1).

It is believed that in developed countries, the most common cause for vitamin B₁₂ deficiency in the elderly is inadequate dietary intake.¹¹,¹³ However, studies have shown that this is far from real. A French study showed that among 172 elderly patients with vitamin B₁₂ deficiency, only 2% accounted for inadequate intake,²⁶ while in a hospital-based Chinese study on 52 patients, only 3.8% (median age, 73.5 years) with megaloblastic anaemia (98% had vitamin B₁₂ deficiency) had inadequate dietary intake.²⁷ However, this can be a problem in strict vegans because animal products are the only dietary source of vitamin B₁₂. Usually, 2 to 3 mg of vitamin B₁₂ reserves are stored in the body primarily in the liver, and our daily requirement of vitamin B₁₂ is only about 2 to 3 μg. Thus, even with vegan diets, deficiency generally takes several years to develop. According to a local study on 119 older Chinese vegetarian women, the

**Table 1. Causes of vitamin B₁₂ deficiency**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Particulars</th>
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<tbody>
<tr>
<td>Inadequate intake</td>
<td>Alcohol consumption</td>
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<tr>
<td></td>
<td>Vegetarian diet</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Food vitamin B₁₂ malabsorption</td>
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<tr>
<td></td>
<td>Lack of intrinsic factor or parietal cell</td>
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<tr>
<td></td>
<td>• Pernicious anaemia</td>
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<tr>
<td></td>
<td>• Atrophic gastritis</td>
</tr>
<tr>
<td></td>
<td>• Post-gastrectomy</td>
</tr>
<tr>
<td>Ileal malabsorption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ileal resection</td>
</tr>
<tr>
<td></td>
<td>• Crohn’s disease</td>
</tr>
<tr>
<td>Defective transport</td>
<td>Transcobalamin deficiency (genetic)</td>
</tr>
</tbody>
</table>
prevalence of deficiency was 42%.26 Besides, factors like poor health conditions, especially in those living in institutions, lead to inadequate nutritional intake and vitamin B₁₂ deficiency.

Often, vitamin B₁₂ deficiency can be seen even among the elderly consuming meat and animal proteins and this is because of malabsorption. Vitamin B₁₂ in animal food is bound to a protein, and after ingestion, it is broken down in the stomach by pepsin and hydrochloric acid to release free vitamin B₁₂ (Fig 13). The free vitamin B₁₂ is then bound to R-protein (transcobalamin I) found in saliva and gastric juice. The vitamin B₁₂–R-protein complex is also secreted in bile from the enterohepatic circulation. These complexes are then degraded by pancreatic enzyme to release free vitamin B₁₂ in the duodenum. The free vitamin B₁₂ is then bound to intrinsic factor secreted by the gastric parietal cells, and then they travel undisturbed until the distal 80 cm of ileum where they bind to mucosal cell receptors. Subsequently, vitamin B₁₂ is carried by transport protein, transcobalamin, via the portal system to all cells in the body for utilisation. About 60% of vitamin B₁₂ from food is absorbed through this pathway, and any pathophysiological changes in stomach, pancreas, and intestine result in disturbance of vitamin B₁₂ absorption. Food-cobalamin (vitamin B₁₂) malabsorption, first described by Carmel in 1995,30 is the most common cause of vitamin B₁₂ deficiency in the elderly and accounts for about 40% to 70% of cases.26,29,31 It is characterised by the inability to release vitamin B₁₂ from food or from its binding protein and thus, preventing vitamin B₁₂ from being taken up by intrinsic factor for absorption. It is defined by vitamin B₁₂ deficiency in the presence of sufficient dietary vitamin B₁₂ intake, negative Schilling test, and lack of anti-intrinsic factor antibodies.30 Clinically, it is diagnosed by exclusion of other disorders or factors causing vitamin B₁₂ deficiency. It can be corrected simply with oral vitamin B₁₂ supplement since free vitamin B₁₂ absorption is not affected.31 Any process that interferes with the release of free vitamin B₁₂, such as decreased production of gastric acid and pepsin for releasing vitamin B₁₂ from food, and impaired secretion of pancreatic enzyme for releasing vitamin B₁₂ from vitamin B₁₂–R-protein complex, can lead to malabsorption. Atrophic gastritis is the main cause of food-cobalamin malabsorption in the elderly. In the stomach, hypochlorhydria associated with atrophic gastritis interferes with vitamin B₁₂ release from the food and causes intestinal bacterial overgrowth to compete for vitamin B₁₂ uptake, resulting in a decline in vitamin B₁₂ in the body. The prevalence of atrophic gastritis in the elderly ranges from 20% to 50% and generally increases with age.26,32 According to Framingham Heart Study, the prevalence in age-group of 60 to 69 years was 24% and increased to 37% in people aged >80 years.33 Chronic Helicobacter pylori infection is strongly associated with atrophic gastritis,34,35 and a study reported that H pylori was found in 56% of people with vitamin B₁₂ deficiency.36 Other causes of food-cobalamin malabsorption include long-term consumption of proton pump inhibitors,28 histamine H₂ blockers,26 chronic alcohol consumption, gastric bypass surgery, and pancreatic insufficiency in patients with alcohol abuse and cystic fibrosis. Food-cobalamin malabsorption often produces a slow, progressive depletion of vitamin B₁₂. Clinical manifestations tend to be subtle and mild,2 although progression to more severe form, like pernicious anaemia (PA), can still occur in a minority of patients.26

Pernicious anaemia, a result of autoimmune atrophic gastritis (type A atrophic gastritis), is most often diagnosed in the elderly. Earlier studies suggested that PA was restricted to Northern Europeans, but subsequent studies indicate that PA affects virtually all ethnic groups.37 Pernicious anaemia was considered a classical cause of vitamin B₁₂ deficiency before food-cobalamin malabsorption was described, and accounted for 15% to 25% of vitamin B₁₂ deficiency in the elderly in studies.9 In a local study on 296 Chinese patients, definite PA was diagnosed in 61% of patients having megaloblastic anaemia with vitamin B₁₂ or folate deficiency.38 Pernicious anaemia is characterised by destruction of gastric mucosa, especially fundal mucosa, primarily by a cell-mediated mechanism.39 There is progressive destruction and eventual loss of intrinsic factor producing gastric parietal cells. Moreover, auto-antibodies in gastric juices bind and block the vitamin B₁₂–binding site of intrinsic factor and prevents the uptake of vitamin B₁₂. The end result is gastric atrophy and depletion of intrinsic factor leading to poor absorption of food-bound, free, and biliary vitamin B₁₂.32 Malabsorption is more complete and severe in PA compared to food-cobalamin malabsorption which is more partial in nature,2 and so the manifestations are more overt and severe in PA. Two antibodies, anti-parietal cell antibody and anti-intrinsic factor antibody, have been described in PA. Anti-parietal cell antibody is more sensitive (90%) but less specific (50%) for diagnosis of PA as it can also be found in other autoimmune diseases.20,39 On the other hand, anti-intrinsic factor antibody is less sensitive (50%) but more specific (98%), and its presence is almost diagnostic of PA.20,39 Schilling test, traditionally used to diagnose intrinsic factor–related malabsorption, is now rarely performed. Although PA is associated with excess risk of gastric carcinoma and gastric carcinoid tumour,40 the benefit of endoscopic surveillance has still not been established. Once the patient is diagnosed with PA, single endoscopic screening for gastric cancer or carcinoid tumours is recommended, but subsequent
routine endoscopic surveillance recommendation is inconclusive. In the elderly, long-term use of medications for co-morbidities can interfere or reduce vitamin $B_{12}$ absorption. These include proton pump inhibitors and histamine $H_2$ blockers, which suppress gastric acid secretion and prevent release of vitamin $B_{12}$ from food. Other drugs like metformin reduces intestinal availability of free calcium ions for vitamin $B_{12}$—intrinsic factor complex uptake by ileal cell membrane receptors, and cholestyramine interferes with vitamin $B_{12}$ absorption from intestine.

**Clinical manifestations of vitamin $B_{12}$ deficiency**

Vitamin $B_{12}$ is essential for metabolism of all cells in our body. In humans, two enzymatic reactions are dependent on vitamin $B_{12}$—methylmalonyl coenzyme A mutase (MUT) reaction and 5-methyltetrahydrofolate–homocysteine methyltransferase (MTR) reaction (Fig 2). The MUT reaction is an important step in the extraction of energy from protein and fat in the mitochondrial citric acid cycle. In the MTR reaction, vitamin $B_{12}$ and folic acid are required for the conversion of homocysteine to methionine that is important for maintaining the integrity of nervous system. Tetrahydrofolate is also regenerated via the MTR reaction for DNA synthesis. Hence, in vitamin $B_{12}$ deficiency, multi-organ systems can be affected and hence associated with wide spectrum of clinical manifestations. However, clinically overt vitamin $B_{12}$ deficiency with classical feature of macrocytic anaemia and neuropathy is infrequently seen in the elderly. Very often they have mild, subclinical deficiency, which are usually asymptomatic.

**Clinical manifestations of vitamin $B_{12}$ deficiency are usually non-specific and are highly variable according to severity or organ systems involved. There is no one clinical feature unique to all patients with vitamin $B_{12}$ deficiency. Non-specific symptoms and signs are loss of appetite, diarrhoea, fatigue and weakness, shortness of breath, low blood pressure, confusion, and change in mental states. Classical manifestations include Hunter’s glossitis, megaloblastic anaemia, and subacute combined degeneration of spinal cord (Table 2).**

**Vitamin $B_{12}$ deficiency and atherosclerotic vascular disease**

Hyperhomocysteinaemia, as an independent risk factor for cardiovascular disease, has been receiving increased attention. Elevated homocysteine level is associated with an increased risk for atherosclerotic and thrombotic events. Meta-analysis of 30 studies involving 5073 ischaemic heart disease (IHD) events suggested that elevated homocysteine level was at most a modest independent predictor of IHD and stroke risk in healthy populations, and a 25% reduction in homocysteine levels was associated with 11% and 19% reduction in IHD and stroke, respectively. Another meta-analysis also provided a strong evidence of the causal association between homocysteine and cardiovascular disease, and

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**TABLE 2. Clinical manifestations of vitamin $B_{12}$ deficiency**

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological</td>
<td>Macrocytosis (frequent)</td>
</tr>
<tr>
<td></td>
<td>Isolated thrombocytopenia and neutropenia, pancytopenia (rare)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Combined degeneration of the cord (classic)</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy (frequency)</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
</tr>
<tr>
<td></td>
<td>Optic atrophy (rare)</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>Psychosis, depression</td>
</tr>
<tr>
<td>Digestive</td>
<td>Hunter’s glossitis, angular stomatitis, jaundice, lactate and bilirubin elevation (classic)</td>
</tr>
<tr>
<td>Hyperhomocysteinaemia</td>
<td>Cardiovascular and thromboembolic risk</td>
</tr>
</tbody>
</table>

* Adapted from Reference 9
showed that lowering homocysteine level by 3 μmol/L could reduce the risk of IHD by 16% and stroke by 24%.47

Vitamin B12, folic acid, and vitamin B6 are required for homocysteine metabolism, and often nutritional deficiency of these vitamins can cause hyperhomocysteinaemia. In contrast to severe hyperhomocysteinaemia associated with genetic disorders, hyperhomocysteinaemia resulted from nutritional deficiency is mild but is still associated with increased risk of atherothrombosis. The proposed mechanism for hyperhomocysteinaemia on inducing endothelial dysfunction and thus atherosclerosis includes homocysteine-induced endoplasmic reticulum stress, oxidative stress, and proinflammatory response.48 Animal models of hyperhomocysteinaemia have confirmed the causal relationship between hyperhomocysteinaemia and the development of endothelial dysfunction and accelerated atherosclerosis.48

Although meta-analyses have shown reduction of cardiovascular risk with reduction of homocysteine levels,46,47 vitamin supplementation (with vitamin B6, vitamin B12, and folic acid) to lower homocysteine in the body may not be transformed into clinically beneficial vascular outcomes. In a double-blind, randomised controlled trial of 3680 adults with non-disabling cerebral infarction, subjects who received a combination of vitamin B12, vitamin B6, and folic acid showed moderate reduction in total homocysteine levels, but there was no effect on vascular outcomes (recurrent ischaemic stroke and coronary heart disease) during 2 years of follow-up.49 Probably a longer duration of treatment may be necessary or there may be other factors governing the clinical response. Therefore, we need more controlled trials to explore the vascular benefits of vitamin supplementation.

Vitamin B12 deficiency and neuropsychiatric illness

Neuropsychiatric manifestations in the absence of haematological abnormalities are commonly seen in the elderly.2,50 These include paraesthesia, weakness, gait abnormalities, and cognitive or behavioural changes. Although the exact mechanism of how vitamin B12 deficiency causes neuropsychiatric disorder is unclear, the disruption of both MUT and MTR vitamin B12–dependent reactions seem to play a role. Vitamin B12 deficiency disrupts MUT reaction with accumulation of MMA; MMA is a myelin destabiliser and can affect normal myelin formation. Besides, disruption of MTR reaction leads to insufficient supply of methionine and S-adenosylmethionine (SAM), which is essential for the myelination of myelin sheath, phospholipids and neurotransmitter synthesis, for maintaining brain and nervous system function.51 Furthermore, high levels of homocysteine due to vitamin B12 deficiency are associated with an increased risk of atherosclerotic vascular disease, and this in turn may increase the risk of cognitive impairment or dementia. It has been shown that low serum vitamin B12 is associated with a 2- to 4-fold higher risk of cognitive impairment.52

The prevalence of low serum vitamin B12 has been reported to be significantly higher in the people with Alzheimer’s disease (AD).52 However, the causal relationship between vitamin B12 deficiency and the development of AD remains controversial. Amyloid deposition and hyperphosphorylation of tau protein are believed to be involved in the mechanism of AD. The SAM-dependent methylation is involved in the regulation of mechanism of presenilin I expression, γ-secretase activity, and thus amyloid levels; SAM is also involved in the regulation of tau phosphorylation.51 Moreover, hyperhomocysteinaemia has been shown to be associated with a significant increase in amyloid level and amyloid deposition on cortex and hippocampus in mouse models of AD.53 Overall, vitamin B12 deficiency may have implications in the neuropathological process of AD.

Depression is a common psychiatric manifestation of vitamin B12 deficiency. Involved in the synthesis of neurotransmitters, SAM may be implicated in mood disorders. In a population-based study of 3884 elderly people, deficiency of vitamin B12 was associated with almost 70% more likelihood of having a depressive disorder.54 In another cross-sectional study of 700 community-dwelling, physically disabled women aged ≥65 years, vitamin B12-deficient women were twice more likely to have severe depressive symptoms.55 Although controlled studies to show response to vitamin B12 replacement therapy in depression are lacking, it is recommended that all patients with vitamin B12 deficiency should be managed as part of depression treatment. Psychosis, including delusion and hallucination, has also been reported in vitamin B12-deficient patients. Although the exact mechanism is unknown, vitamin B12 replacement even after a prolonged period (at least up to 2 years) has shown good outcomes in patients with psychosis.56

Therapeutic management

In general, vitamin B12 replacement therapy helps to reverse the haematological abnormalities and psychiatric disorders. However, even after correcting serum vitamin B12 and its metabolite levels, or haematological abnormalities, the ability to reverse cognitive impairment (dementia) and neurological disorders is not promising.50-52 The longer the time the neurological disorder or cognitive impairment presents before treatment, the less likely it can be reversed. It is suggested that prompt correction of deficiency should be done within 6 to 12 months of cognitive impairment in order to obtain maximum
response. Nevertheless, continuous replacement therapy may still help to prevent symptoms from deteriorating. Treatment for subtle or subclinical deficiency is still debatable although prompt diagnosis and treatment might prevent the progress to clinically overt deficiency.

Classical treatment for vitamin B₁₂ deficiency is parenteral administration, usually intramuscular injection, to correct the deficiency and build up tissue storage. There are two forms of vitamin B₁₂ for parenteral administration: cyanocobalamin and hydroxocobalamin. It is believed that hydroxocobalamin is converted to active enzyme more easily and retained in the body for a longer period of time than cyanocobalamin, and therefore be administered in intervals of 3 months. The regimen for vitamin B₁₂ therapy varies across countries and between individual practices. Generally, the schedule for vitamin B₁₂ replacement is 1 mg daily for a week or 1 mg 3 times a week for 2 weeks, followed by 1 mg per week for 1 month, and then 1 mg per month as maintenance dose.⁸

Around 1% to 5% of free vitamin B₁₂ can be absorbed along the entire intestine by passive diffusion. Oral vitamin B₁₂ replacement is theoretically as effective as parenteral administration even in patients with PA or ileal disease, provided that the dosage is high. However, the unpredictable absorption by passive diffusion makes recommendation of a standard dose difficult. A Cochrane review supports the use of high-dose vitamin B₁₂ (1 mg and 2 mg daily) in elevating serum vitamin B₁₂ level and achieving haematological and neurological responses, even in patients with PA or with ileal resection.⁵⁸ The recommendation for oral replacement is 1 mg daily for a month, and then 125 to 250 μg daily as maintenance dose for patients with dietary insufficiency and food-cobalamin malabsorption, while for PA the maintenance dose is 1 mg daily.⁵⁹

Vitamin B₁₂ does not have side-effects even when prescribed in large doses.⁵⁹ However, hypokalaemia, resulting from uptake of circulating potassium by newly growing and dividing haematopoietic cells, can be severe or sometimes life-threatening. Transient potassium replacement at the initial stage of vitamin B₁₂ replacement, especially in those with low-normal serum potassium, can prevent subsequent hypokalaemia.

Correction of risk factors associated with vitamin B₁₂ deficiency, like antibiotics for H pylori infection and intestinal bacterial overgrowth, stopping or replacing offending medications are also important in the management and prevention of vitamin B₁₂ deficiency. Some institutions have even recommended universal vitamin B₁₂ supplementation for people aged ≥60 years in view of the high prevalence of vitamin B₁₂ deficiency among this population.¹⁵

Conclusion

Vitamin B₁₂ deficiency is prevalent among the elderly. Elderly people are particularly at risk of deficiency because of the increasing prevalence with increasing age of atrophic gastritis-associated food-cobalamin malabsorption, PA, and due to drug intake for co-morbidities. Symptoms and signs of vitamin B₁₂ deficiency are usually vague and unrecognised. Treatment may always be useful to correct clinical abnormalities like vitamin B₁₂–related haematological abnormalities, psychiatric and depressive symptoms. For neurological disease and dementia, prompt vitamin replacement is necessary before it becomes irreversible or permanent. Both oral and parenteral administration of vitamin B₁₂ are effective and without untoward side-effects. Overall, we are in support of screening for vitamin B₁₂ deficiency in the elderly. However, accurate diagnosis of vitamin B₁₂ deficiency remains controversial. To diagnose vitamin B₁₂ deficiency, laboratory tests have their limitations, and this makes it difficult to choose a reliable and easily available tool for screening. Although there is no formal recommendation for screening for vitamin B₁₂ deficiency in asymptomatic elderly people, the high prevalence, higher risk of deficiency in the elderly, easy and safe treatment availability warrant more liberal testing and vitamin supplementation in the elderly.

References


