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Original Article

# Vitamin $B_{12}$ deficiency common in primary hypothyroidism

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## Abstract

**Objective:** To assess the prevalence and clinical features of $B_{12}$ deficiency in hypothyroid patients and to evaluate clinical response in symptoms to B12 replacement therapy.

**Methods:** One hundred and sixteen hypothyroid patients from our endocrine clinic were evaluated for signs and symptoms of vitamin $B_{12}$ deficiency. Laboratory parameters including Haemoglobin (Hb), MCV, Vitamin $B_{12}$ levels and presence of anti thyroid antibodies were analyzed. Patients with low $B_{12}$ levels were treated with parenteral intramuscular vitamin $B_{12}$ monthly, and monitored for improvement of symptoms.

**Results:** A total of 116 patients (95 females and 21 males) were evaluated. Forty six (39.6%) hypothyroid patients had low vitamin $B_{12}$ levels. Males and females had the same prevalence of $B_{12}$ deficiency. Generalized weakness, impaired memory, depression, numbness and decreased reflexes were more frequently noted in $B_{12}$ deficient patients, but failed to achieve statistical significance when compared with $B_{12}$ sufficient patients. The mean Hb in $B_{12}$ deficient group was 11.9±1.6 mg/dl and 12.4 ± 1.7 mg/dl in the B12 sufficient group, however the mean MCV did not differ in the two groups. Patients with B12 deficiency did not have a higher prevalence of anaemia. Thyroid antibodies were checked in half the patients and 67% had positive titers for anti thyroid antibodies. Prevalence of vitamin B12 deficiency did not differ in patients with positive antibodies (43.2%) compared to those with negative antibodies (38.9%) (p= 0.759). Twenty four hypothyroid patients with $B_{12}$ deficiency received intramuscular vitamin $B_{12}$ injections monthly and improvement in symptoms was noted in 58.3% of these subjects. Additionally, 21 subjects complained of symptoms consistent with B12 deficiency but who had normal range $B_{12}$ levels and were prescribed monthly $B_{12}$ injections and 8 (40%) had good subjective clinical response at 6 months.

**Conclusions:** There is a high (approx 40%) prevalence of B12 deficiency in hypothyroid patients. Traditional symptoms are not a good guide to determining presence of $B_{12}$ deficiency. Screening for vitamin $B_{12}$ levels should be undertaken in all hypothyroid patients, irrespective of their thyroid antibody status. Replacement of $B_{12}$ leads to improvement in symptoms, although a placebo effect cannot be excluded, as a number of patients without $B_{12}$ deficiency also appeared to respond to $B_{12}$ administration (JPMA 58:258;2008).

## Introduction

Vitamin $B_{12}$ (cyanocobalamin) deficiency occurs in 3-4% of the general population.[1] The prevalence is reported to be higher (15-25%) among nursing home residents.[2] Pernicious anaemia is present more frequently in subjects with primary autoimmune hypothyroidism with reports of association in up to 12% of hypothyroid patients.[3] Antibodies to gastric parietal cells are seen in 1/3 rd of patients with primary hypothyroidism. Vitamin $B_{12}$ deficiency in hypothyroid patients may also be due to other causes, including inadequate intake or altered intestinal absorption due to sluggish bowel motility, bowel wall oedema and bacterial overgrowth. Non autoimmune causes of $B_{12}$ deficiency in hypothyroid patients have not been evaluated in detail and may vary according to dietary habits in different population groups. Hypothyroid patients often present with symptoms of paraesthesia, numbness, weakness and poor memory, despite being on adequate replacement doses of thyroxine. We noted these symptoms to be common among our hypothyroid patients and hence undertook to evaluate vitamin

$B_{12}$ levels in patients with primary hypothyroidism.

## Patients and Methods

Patients with primary hypothyroidism who attended the endocrine clinic at Aga Khan University Hospital, Karachi, Pakistan from January 2001 - December 2001 were evaluated. Patients, who were vegetarian, had a history of gastric or ileal resection, or pancreatic insufficiency were excluded. Clinical features including weakness, numbness, diarrhoea, abdominal pain, impairment of memory, parasthesias, dysphagia, dizziness and depression were noted. Concomitant illnesses and medications including use of metformin and gastric acid inhibitors were noted. Presence of pallor, inflammation of tongue, impaired vibration or position sense, reflexes and presence of splenomegaly were recorded. Haemoglobin (Hb), mean corpuscular volume (MCV), anti thyroid antibodies, thyroid function tests and vitamin $B_{12}$ levels were measured. Patients with low $B_{12}$ levels or who had suggestive symptoms were treated with monthly intramuscular vitamin $B_{12}$ injections. The patients were followed for 6 months after institution of $B_{12}$ replacement and self reported change in symptoms was noted.

Haemoglobin was checked by Coulter counter. Vitamin $B_{12}$ levels were estimated by RIA (radioimmunoassay) on a gamma counter by the diagnostic product cooperation (DPC), the normal range being 200 to 900 pg/ml. Thyroid antibodies were checked by the haemagglutination method by Remel and positive tests were then diluted and results were reported accordingly.

Results were expressed as mean ± standard deviation, median for all continuous variables and number (percentage) for categorical data. Univariate analysis was performed by using the independent sample t -test, Mann Whitney U test, Pearson Chi-square test and Fisher Exact test whenever appropriate. A p value <0.05 was considered statistically significant and was two sided. Statistical interpretation of data was performed using SPSS 10.0

## Results

Of the 116 hypothyroid patients evaluated, 95 (81.8%) were females and 21 (18.2%) were males. Patients' ages ranged from 19 to 91 years. The mean age was 44 ±13.7 years (53.6 ± 12.3 for males and 41.9 ± 13.1 years for females). Fifty percent of the patients (58/116) were under 40 years of age. Forty seven (40.5%) had $B_{12}$ levels <200 pg/ml (normal 200-900pg/ml). Of these, 31 had $B_{12}$ levels between 100 and 200 pg/ml and 16 patients had $B_{12}$ <100pg/ml. No difference in mean age and sex ratios between groups with Vitamin $B_{12}$ deficiency and those with normal $B_{12}$ levels were noted (Table1).

Symptoms of numbness, paraesthesia and dysphagia were seen more commonly in $B_{12}$ deficient patients compared to $B_{12}$ sufficient patients. The frequency of the commonly recognized symptoms associated with vitamin $B_{12}$ deficiency among our hypothyroid patients is noted in Table 2. Two hypothyroid patients with $B_{12}$ deficiency were noted to have glossitis. Impaired vibration or position sense was not recorded in any of the $B_{12}$ deficient patients. There were more patients with impaired vibration sense and diminished lower extremity reflexes in the $B_{12}$ sufficient group. The frequency of abnormal signs is noted in Table 3.

Haemoglobin values were noted in 87 patients. The mean haemoglobin in the $B_{12}$ deficient group was slightly lower than in the normal $B_{12}$ group (11.9±1.6 g/dL vs 12.4± 1.7 g/dL). Overall 42% of the males had Hb <13.5 g/dL while 23.5% females had Hb <11 g/dL. Hypothyroid patients with $B_{12}$

**Table 1. Age and sex disribution amongst $B_{12}$ deficient and non deficient patients.**

| | $B_{12}$ >200 pg/ml | $B_{12}$<200pg/ml |
|---|---|---|
| No. | 69 | 47 |
| Age | 44.9 ± 14.3 yrs | 42.7±12.7 yrs. |
| Sex | M 12 (17.4%) | M 9 (19.1%) |
| | F 57 (82.6%) | F 38 (80.8%) |

**Table 2. Frequency of symptoms in hypothyroid patients with low and normal $B_{12}$ levels.**

| Symptom | Total No. | $B_{12}$ <200pg/ml | $B_{12}$>200pg/ml |
|---|---|---|---|
| Weakness | 61/113 | 26 (42.6%) | 35(57.4%) |
| Numbness | 22/109 | 12 (54.5%) | 10 (45.5%) |
| Diarrhoea | 6/113 | 2 (33.3%) | 4 (66.7%) |
| Abdominal pain | 21/114 | 9 (42.9%) | 12 (57.1%) |
| Impaired memory | 11/114 | 3 (27.3%) | 8 (72.7%) |
| Fever | 8/116 | 2 (25%) | 6 (75%) |
| Parasthesias | 15/111 | 9 (60%) | 6 (40%) |
| Dysphagia | 15/114 | 8 (53.3%) | 7 (46.2%) |
| Dizziness | 26/112 | 8 (30.8%) | 18 (69.2%) |
| Depression | 22/114 | 10 (48.5%) | 12 (52.5%) |

**Table 3. Frequency of abnormal signs in hypothyroid patients with low and normal $B_{12}$ levels.**

| Signs | Number abnormal/ Number tested. | $B_{12}$<200pg/ml | $B_{12}$>200pg/ml |
|---|---|---|---|
| Pallor | 9/102 (8.8%) | 5 (55.6%) | 4 (44.4%) |
| Glossitis | 2/116 (1.7%) | 2 | --- |
| Impaired vibration | 4/57 (7.0%) | --- | 4 |
| Impaired position | 1/63 (1.5%) | --- | 1 |
| Impaired reflexes | 23/71 (32.3%) | 6 (26.1%) | 17(73.9%) |
| Splenomegaly | 1/116 (0.86%) | --- | 1 |

were not noted to have an increased prevalence of anaemia than the non deficient group in both sexes. The MCV was checked in 44 patients, 15 who were $B_{12}$ deficient and 29 were not The mean MCV in both groups was not different (84.23± 7.25 fL vs 84.97± 7.36 fL).Antimicrosomal and antithyroglobulin antibodies were checked in 55 and 53 patients respectively. Antimicrosomal antibodies were positive in a total of 37/55 (67.2%) patients. Of these 16/37 (43.2%) were $B_{12}$ deficient and 21/37 (56.7%) were B12 sufficient. Antithyroglobulin antibodies were positive in 32/53 (60.3%) patients 16 each in $B_{12}$ deficient and sufficient group. They were negative in 21/53 (39.7%) patients. There was no association noted between $B_{12}$ status and presence of thyroid antibodies.

Associated diseases among the 116 hypothyroid patients included diabetes mellitus (19 patients), hypertension (20 patients), ischaemic heart disease (11 patients) and dyslipidemia (23 patients). Six of the 19 diabetic patients (31.6%) were $B_{12}$ deficient. Four of these individuals were on metformin which may have contributed to $B_{12}$ deficiency. Four of 17 patients on proton pump inhibitors or H2 receptor blockers were found to be B12 deficient

Replacement therapy with intramuscular $B_{12}$ injections was instituted in a total of 45 patients with almost equal number of patients in the $B_{12}$ deficient (24 patients) and non deficient patients (21 patients) who had symptoms suggestive of $B_{12}$ deficiency. Improvement in symptoms were documented in a total of 36 patients of which 21 (58.3%) were $B_{12}$ deficient and 15 (41.7%) were not. Nine patients reported no improvement in symptoms, of which 3/9 (33.3%) were deficient of $B_{12}$ and 6/9 (66.6%) were not.

## Discussion

Vitamin $B_{12}$, also known as cobalamin, was first isolated in 1948 and soon after found to be effective in treatment of pernicious anaemia. Prevalence of $B_{12}$ deficiency has been reported up to 15-25% in certain population groups particularly in the elderly.[4] We studied prevalence of $B_{12}$ deficiency in hypothyroid patients and found 47 of 116 (40.5%) patients to have low $B_{12}$ levels. Prevalence in males (42.9%) and females (40%) was similar..

Hypothyroidism may be associated with pernicious anaemia as part of the autoimmune polyglandular endocrinopathy.[5] Vitamin $B_{12}$ deficiency may occur as a result of autoimmune pernicious anemia, malabsorption, malnutrition or use of drugs including proton-pump inhibitors, H2 receptor antagonists or metformin.[6,7] Metformin can cause malabsorption secondary to its effect on ileal mucosa or membrane receptors [8,9] . Proton Pump Inhibitors and H2 receptor antagonists cause gastric hypochlorhydria and malabsorption of vitamin $B_{12}$. Untreated helicobacter pylori infection is occasionally associated with $B_{12}$ deficiency.[10-12] In our study we found no association between use of drugs and $B_{12}$ deficiency, although the numbers may not have been large enough to demonstrate this association. Intrinsic factor and gastric parietal cell antibody assays were not available locally at the time of the study, hence while we demonstrated frequent occurrence of $B_{12}$ deficiency in hypothyroid patients, it was not possible to determine the underlying etiology of this association.

Clinical signs of vitamin $B_{12}$ deficiency may take long to manifest and often affected patients are asymptomatic for several years. Occasionally, haematological or neuropsychiatric manifestations may present as early markers of deficiency but many non specific complaints are attributed to aging. The neuropsychiatric features include fatigue, weakness, loss of memory, dementia, and depression.[4] Hypothyroid and $B_{12}$ deficient patients often have common symptoms of weakness, lethargy, memory impairment, numbness and tingling. We noticed that several patients, despite being on adequate thyroxine replacement, had persistence of symptoms and subsequently were found to be $B_{12}$ deficient. In this study, we noted that the complaint of fatigue was common in both patients with normal and low $B_{12}$ levels. Complaints of memory impairment and frequency of depression also did not differ. Differences in frequencies of numbness and paraesthesia did not reach statistical significance between $B_{12}$ sufficient and deficient groups. Anaemia with or without macrocytosis, tend to occur later in $B_{12}$ deficiency. and may be absent in $B_{12}$ deficiency.[13,14] There was a significant improvement reported in symptoms within 3-6 months of initiating $B_{12}$ treatment in hypothyroid individuals with low $B_{12}$ levels. We also noted a high reported level of improvement in similar symptoms in those who were not $B_{12}$ deficient. Hence, a placebo effect may affect the initial reporting of symptoms and a placebo controlled study will be required to determine this

Metabolism of homocystine and methyl-melonyl acid (MMA) involves cobolamin, thus both MMA and homocystine levels increases in vitamin B12 deficiency.[4,15,16] Elevated homocysteine levels have been associated with development of atherosclerosis.[17,18] When homocysteine levels are elevated other causes including coexisting folic acid deficiency, renal impairment and inadequate thyroid replacement need to be evaluated. We did not study homocysteine levels in our hypothyroid patients, but this is an area of increasing interest currently. Studies have shown a relationship between hypothyroidism and hyperhomocysteinemia[16,19-21], which improves with treatment to euthyroid status.

Our study showed vitamin $B_{12}$ deficiency to be common

in this population of hypothyroid patients. Screening for $B_{12}$ deficiency should be undertaken early in the diagnosis of hypothyroidism and periodically thereafter. Patients should be followed and evaluated for suggestive symptoms. Surrogate markers including anaemia and macrocytosis cannot be relied upon to select out likely $B_{12}$ deficient individuals. There is improvement in symptoms after initiating $B_{12}$ treatment in these patients although a placebo effect may exist and larger studies need to be undertaken to evaluate this further. Initiation of early therapy will prevent the long term sequele of vitamin $B_{12}$ deficiency.

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