How often should we trust the low level of vitamin B12?

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Abstract

Vitamin B12 deficiency is very common in clinical practice. The levels of metabolites such as homocysteine and methylmalonic acid increases in Vitamin B12 deficiency. This study aim to demonstrate how often plasma vitamin B12 levels reflect functional B12 deficiency. Homocysteine levels measured in 100 patients who had low plasma vitamin B12 levels. While 59 patients had normal levels, 41 patients had high levels of homocysteine. We found that approximately half of the patients with vitamin B12 deficiency, the serum Vitamin B12 levels doesn’t express tissue B12 level truly. This study demonstrates that value of serum B12 level is a limited method to determine B12 deficiency and it is inappropriate to start long term replacement therapy based on that level. Measuring homocysteine or methylmalonic acid levels with plasma vitamin B12 levels despite the increase in cost, might be supportive for the diagnosis in cases which has borderline levels.

Keywords: vitamin B12 levels, homocysteine

INTRODUCTION

Vitamin B12 deficiency is very common in clinical practice. Vitamin B12 deficiency is important due to association with hematological abnormalities such as anemia, thrombocytopenia, leucopenia, irreversible neurological damage, cardiovascular and cerebrovascular events (Biomarkers of cobalamin, 2011). The levels of metabolites such as homocysteine and methylmalonic acid increases in Vitamin B12 deficiency. But functional B12 deficiency could be diagnosed with elevated homocysteine and methylmalonic acid levels in 10% to 50% of patients who has normal plasma vitamin B12 levels (Pennypacker et al., 1992; Stabler, 1995). In this study we aimed to reveal how often low levels vitamin B12 may reflect functional B12 deficiency with use homocysteine levels.

METHOD

This study has been conducted retrospectively in 100 patients (76 males, 24 females) with B12 deficiency in the hematology outpatient clinic between January –May 2011. By analyzing the homocysteine, folic acid, urea, creatinine levels; patients with pregnancy, chronic renal failure, folic acid deficiency and hereditary thrombophilia (MTHFR) have been excluded from the study. Cases with serum vitamin B12 levels below 221 pg/L have been categorized as low vitamin B12 level. The cut off level of
homocysteine was above 14.5 µmol/L. For statistical analysis SPSS 17.0 has been utilized.

RESULTS

The average age of the patients was between 44.60±17.45. Vitamin B12 levels were between 84-210 pg/L, averaging 163±33.17 pg/L. Homocysteine levels were between 5-48.5 µmol/L. The information related to patient population has been demonstrated in the table. Vitamin B12 replacement therapy has been administered for patients with high levels of homocysteine.

DISCUSSION

Humans are dependent on two enzymatic reactions to vitamin B12. Vitamin B12 plays a role as cofactor to convert homocysteine to methionine. The level of homocysteine increases with the dysfunction of this reaction. Methyl malonic CoA plays a role in the conversion of succinyl CoA as cofactor. Deficiency of vitamin B12 causes serum methylmalonic acid to increase (Robert and David, 2003). Serum and plasma concentration of vitamin B12 show the Vitamin B12 intake and body store. However waiting for B12 level to decrease for the diagnosis of B12 deficiency can cause delays in some cases due to serum B12 levels maintained by tissue B12 stores. Vitamin B12 deficiency diagnosis can be made directly by measuring serum B12; with indirect methods such as anemia, macrocytosis, hypersegmented neutrophils, reticulocytosis, increase in homocysteine and methylmalonic acid levels. Homocysteine and methylmalonic acid levels are crucial due to reflecting tissue vitamin B12 levels (Sumner et al., 1996). MTHFR mutation, hypovolemia and renal insufficiency may affect the level of homocysteine. This should kept in mind while analyzing hyperhomocysteinemia (Green and Jacobsen, 1995; Anne and Per, 1998; Antony, 2005).

There are different ways of measuring Vitamin B12 levels in different laboratories (chemiluminescence, radio assay etc). Despite this, different normal values of Vitamin B12 levels have been set and there is no gold standard (Carmel, 2008). Value of serum B12 level is a limited method to determine B12 deficiency or sufficiency. For example during pregnancy B12 level can be found low (Metz et al., 1995). In one study serum vitamin B12 levels found normal in 5% of patients with documented Vitamin B12 deficiency (Savage et al., 1990). In another study in only 22% of B12 patients whose levels found <180 pg/ml has confirmed diagnosis of Vitamin B12 deficiency. Recommendations based on serum B12 levels are;

- If vitamin B12 level >221 pmol/L is normal, B12 deficiency possibility 1-5%
- Vitamin B12 level (148-241 pmol/L): cut off level, possible B12 deficiency
- Vitamin B12 level < 148 pmol/L: B12 deficiency has been identified (specificity 95-100%)

Despite the increase in cost, measuring the levels of homocysteine might be supportive for the diagnosis in cases which has borderline levels. In one study including 434 patients with low serum vitamin B12 levels, 96% of those have high homocysteine levels (Savage et al., 1994). In our study 41% of patients found to have high homocysteine level. In literature there are different ratios have been reported. Also high homocysteine levels might be found in folic acid deficiency, more reliable results can be achieved via determining methylmalonic acid levels, increasing sample size, standardization vitamin B12 level measurements.

Our country baseline haematological tests are performed in primary care centers. According to the test results patients with low vitamin B12, replacement therapy is given. Despite the normal tissue vitamin B12 levels this patients may receive unnecessary treatment. In this study we want to highlight that serum vitamin B12 level does not reflect tissue level deficiency consistently and it is inappropriate to start long term replacement therapy based on that level. Although methylmalonic acid level is more determining than homocysteine for vitamin B12 deficiency, in this work homocysteine levels were evaluated because of it is more widely studied in our country laboratories.

While evaluating vitamin B12 deficiency to reflect tissue vitamin B12 levels, along with clinical presentation, MCV level, hypersegmentation and reticulocytosis, one should measure homocysteine, methylmalonic acid and holotranscobalamin II levels in centers with measurement capability.

REFERENCES
