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Original Research Article

Vitamin B_{12} and Depression

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Abstract

Depression is a real illness that impacts the brain: It is a serious illness caused by changes in brain chemistry. Research tells us that other factors contribute to the onset of depression, including genetics, changes in hormone levels, certain medical conditions, stress, grief or difficult life circumstances. Any of these factors alone or in combination can precipitate changes in brain chemistry that lead to depression's many symptoms. Preliminary results suggest a relationship between vitamin B12 deficiency and increased levels of fatigue and depression in stroke patients. If these findings could be replicated in a larger and general stroke sample, this would open treatment options and may improve quality of life after stroke. High vitamin B-12 status may be associated with better treatment outcome of depression. One possible connection is the effect of vitamin B-12 on the levels of serotonin in your brain, in addition to other chemicals. Serotonin helps to regulate your mood. Low levels of serotonin may be linked to depression. However, recent research has suggested that serotonin may play a smaller role in depression than previously thought. ***Background/Objective:*** Recent literature has identified links between vitamin B12 deficiency and depression. We compared the clinical response of SSRI-monotherapy with that of B12-augmentation in a sample of depressed patients with low normal B12 levels who responded inadequately to the first trial with the SSRIs. ***Methods:*** Patients with depression and low normal B12 levels were randomized to a control arm (antidepressant only) or treatment arm (antidepressants and injectable vitamin B12 supplementation). The researchers suggest people with depression take a 1-milligram supplement of B-12 daily. More research is needed to fully understand the link between B-12 and depression. ***Results:*** A total of 100 depressed patients were screened. Out of 76 patients with low normal B12 levels (76%) were randomized to the treatment group while 24 (24%) were randomized to the control arm. At three months follow up 100% of the treatment group showed at least a 20% reduction in HAM-D score, while only 69% in the control arm showed at least a 20% reduction in HAM-D score ($p<0.001$). The findings remained significant after adjusting for baseline HAM-D score ($p=0.001$). Hamilton Rating Scale for Depression the Hamilton Rating Scale for Depression (HRSD), also called the Hamilton Depression Rating Scale (HDRS), abbreviated HAM-D, is a multiple item questionnaire used to provide an indication of depression, and as a guide to evaluate recovery.

Keywords: Depression, vitamin B12, antidepressants, RCT.

INTRODUCTION

Vitamin B-12 and other B vitamins play a role in producing brain chemicals that affect mood and other brain functions. Low levels of B-12 and other B vitamins such as vitamin B-6 and folate may be linked to depression. Low levels of a vitamin can result from eating a poor diet or not being able to absorb the vitamins you consume [1]. Older adults, vegetarians and people with digestive disorders such as celiac disease or Crohn's disease may have trouble getting enough B-12. Sometimes a vitamin B-12 deficiency occurs for unknown reasons. If one has vitamin B-12 deficiency, taking a daily supplement that includes vitamin B-12 may help body get the nutrients it needs. But study results have been mixed and questionable on whether vitamin B-12 supplements can help reduce the risk of depression. B-12 and other vitamin supplements can interact with some medications, especially in high doses [2]. There are two types of B12 deficiency, a deficiency that's related to poor intake – so there isn't enough B12 in diet; and then there's a deficiency that's related to poor absorption – so you're eating B12, but you're not absorbing it." B12 shots are recommended, in particular, for those who don't have a protein called intrinsic factor that helps the intestines to absorb the vitamin [3]. "If you don't have that protein you get a deficiency that has to be replaced with a shot," El-Mallakh says. For individuals with this condition, referred to as pernicious anemia – in which the body isn't able to make enough healthy red blood cells – it's usually recommended they get a B12 shot once a month [4]. The best way to get enough B-12 and other vitamins is to eat a healthy diet that includes sources of essential nutrients. Vitamin B-12 is plentiful in animal

products such as fish, lean meat, poultry, eggs, and low-fat and fat-free milk. Fortified breakfast cereals also are a good source of B-12 and other B vitamins. Keep in mind, the role of B vitamins in depression isn't clear and more research is needed [5]. And no supplement can replace proven depression treatments such as antidepressants and psychological counseling. Due to its role in energy metabolism, vitamin B12 is frequently promoted as an energy enhancer and an athletic performance and endurance booster," the NIH notes [6]. "These claims are based on the fact that correcting the megaloblastic anemia caused by vitamin B12 deficiency should improve the associated symptoms of fatigue and weakness. However, vitamin B12 supplementation appears to have no beneficial effect on performance in the absence of a nutritional deficit." Similarly, for a person who is depressed who has normal B12 levels – which can be checked with a blood test – it's not recommended they take a B12 supplement or get a B12 shot [7]. A couple long-term studies have found that regular dosing of vitamin B12 may reduce relapse rates of depression," Frye says. "When we see an abnormality, we want to treat it, recognizing that there is a nutritional deficit that in some way is impacting brain neurotransmission. But we would never have that be a primary focus of treatment for depression, or an exclusive focus for treatment of depression [8]." In short, if you're depressed, experts don't advise shelving traditional treatment, such as medication and therapy, in favor of focusing on B12 supplementation instead. Rather, it's suggested that B12 deficits be addressed as part of a well-rounded approach to improving overall wellness. That can also dovetail into a discussion (for those whose B12 deficit is diet-related) about how dietary improvements can be helpful to bolster mental and physical health [9].

Materials and Methods

A list of 100 target terms related to different types of chronic pain were identified from the following categories: (1) antidepressants, (2) neuropathic drugs, (3) other pharmaceuticals (antihistamines and anti-acids), (4) descriptions of pain, (5) disorders related to excess acid, (6) over the counter antacids, (7) psychotherapy, and (8) medical cannabis. The study was designed as an open label randomized controlled trial at GMC, Amritsar. Low normal B12 level was defined as B12 level ranging between 190 and 300 pg/ml [10]. Patients with B12 deficiency (level below190 pg/ml) were not enrolled due to ethical reasons (patients with established B12 deficiency must be treated and not subjected to randomization).

Results

A total of 199 depressed patients were screened for the B12 levels. Vitamin B12 deficiency was present in 44 (22%) patients; 73 (36%) had low normal B12 levels and 82 (42%) had normal B12 levels. Patients with low B12 levels were given the prescriptions for B12 replacement therapy in addition to the antidepressants. These patients were not randomized. Out of 73 patients with low normal B12 levels 34 (47%) were randomized to the treatment group while 39 (53%) were randomized to the control arm. There were no significant differences between the two groups at baseline except for the higher depression scores in the treatment group (Table -**1**). No adverse effects or complications were noted in either group. For the primary outcome of 20% reduction in HAM-D score, significantly more subjects from the treatment group showed a 20% reduction unadjusted for baseline HAM-D score (100% vs. 69%; $p < 0.001$) [11]. Examining a50% reduction from baseline, this effect remained significant (44% vs. 5%; $p < 0.001$). We also adjusted the analyses of reduction for the baseline HAM-D score and our findings remained significant (Table-**2**). Additionally, the change in HAM-D score was significantly greater for the treatment group, unadjusted and adjusted for the baseline HAM-D score (Table-**2**).

Table-1: Baseline Characteristics Shown as Mean ± Standard Deviation or Frequency (Percent)

Treatment (n=34)	Control (n=39)	p-value	Treatment (n=34)
Age, in years	37.68 ± 13.38	36.56 ± 12.28	0.71
Total HAM-D	23.21 ± 5.85	19.38 ± 5.70	0.006
Vitamin B12 level	238.49 ± 33.21	245.16 ± 27.82	0.36
Male	18 (52.9)	20 (51.3)	0.89
Female	16 (47.1)	19 (48.7)	Female
Marital status			
Single never married	9 (26.5)	13 (33.3)	0.84
Married	21 (61.8)	21 (53.9)	Married
Divorced/separated/widowed	4 (11.8)	5 (12.8)	

Table-2: Outcomes for Follow up After 3 Months Shown as Mean ± Standard Deviation or Frequency (Percent)

Treatment (n=34)	Control (n=39)	Unadjusted P-value	Adjusted* P-value
20% reduction in HAM-D score	34 (100)	27 (69.2)	<0.001
50% reduction in HAM-D score	15 (44.1)	2 (5.1)	<0.001
Follow up HAM-D score	12.12 ± 5.12	14.38 ± 4.73	0.053
Change in HAM-D score	11.09 ± 4.58	5.00 ± 3.38	<0.001

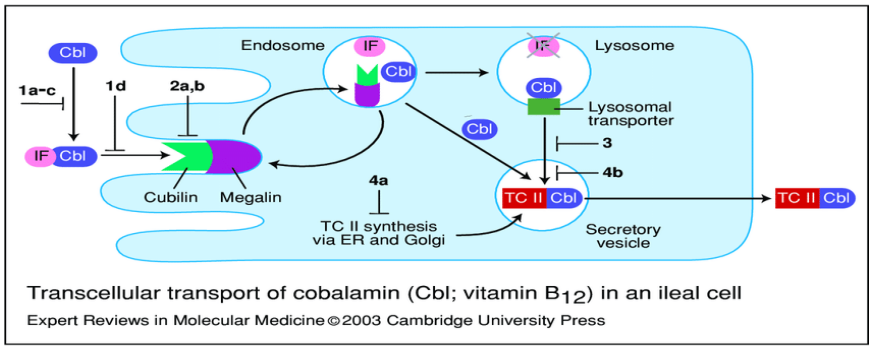

Fig-1:

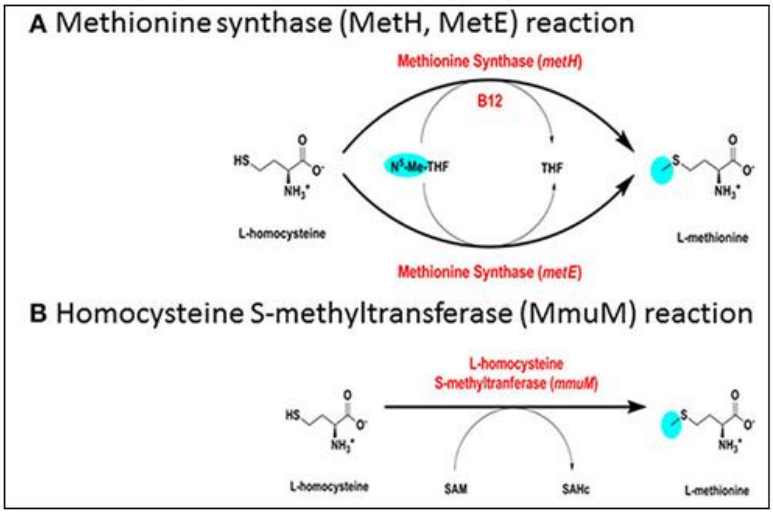

Fig-2:

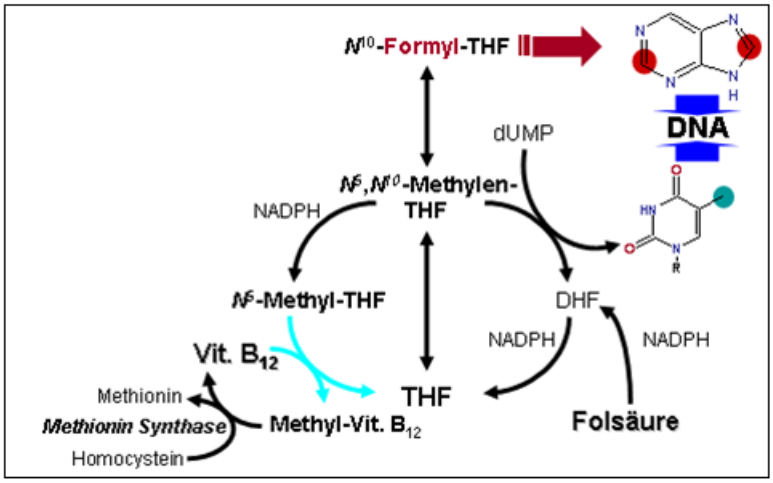

Fig-3: Metabolic Role of Vitamin B_{12}

DISCUSSION

Coexistence of depression and vitamin B12 deficiency are not uncommon. These patients are routinely treated with SSRI and B12 supplementation, however it is not well established whether the people with low normal B12 and co-occurring depression should also receive B12 supplementation. Our study tried to address this issue. Despite not attaining the targeted sample size, the findings appear significant. Vitamin B12 deficiency was present in 22% of our depressed population. This frequency is high in a non-vegetarian, relatively young, middle to upper income population of our patients. A recent study of healthy adults from Karachi showed a population based prevalence of vitamin B12 deficiency (less than 200 pg/ml) in 9.74% people [12]. These findings indicate a substantial co-morbidity of B12 deficiency (22%) in our depressed patient population. We did not randomize B12 deficient patients due to ethical reasons. Low normal B12 levels were present in 36% of patients.

These patients are often not treated with B12 supplementation [13]. The findings of our study clearly indicate that these patients demonstrated significant improvement with B12 supplementation in addition to SSRI as compared to the control group even after adjustment for baseline HAM-D score. We think that these patients represent sub group within the clinically depressed population and a supplementation with B12 along with the conventional antidepressants may be a useful strategy in the treatment of depression in such cases. The work up to diagnose Cyanocobalamin deficiency should begin with a through evaluation of a peripheral smear to diagnose the type of anemia. Cyanocobalamin deficiency characteristically produces a megaloblastic picture with macro-ovalocytosis and hypersegmented neutrophils (polymorphs). The mean corpuscular volume (MCV) is greater than 100 fl and at least one neutrophil should have six or more lobes. Leucopenia, thrombocytopenia, increased lactic acid dehydrogenase and increased bilirubin all reflect ineffective hematopoiesis. Serum vitamin B-12 level should be measured (normal between 200-900 pg/ml). If it is in the low normal range and the index of suspicion is high serum methyl-malonic acid and homocysteine levels can be measured and these will be found to be elevated. Elevated serum gastrin levels with achlorohydria points towards pernicious anemia as the cause of vitamin B-12 deficiency. Serum antibodies to intrinsic factor and anti-parietal cell antibodies can be measured too. Low holotranscobalamin II level is a sensitive indicator of vitamin B-12 deficiency though currently the test is available only in research centers. Shilling's test helps to rule out Cyanocobalamin deficiency due to intrinsic factor deficiency. In this test radio labeled cobalamin is given by mouth after the patient's intrahepatic stores have been saturated by an intramuscular injection of unlabeled cobalamin. The excretion of radio labeled cobalamin is measured in the urine. If this test is abnormal the test is repeated with radio labeled cobalamin bound to intrinsic factor given orally. If the patient has a deficiency of intrinsic factor (pernicious anemia) the absorption will be normal. Magnetic resonance imaging may show T-2 weighted hyperintensities involving the posterior columns especially in the cervical region and EMG may show evidence of motor and sensory axonopathy.

CONCLUSION

These findings have important clinical implications. B12 deficiency and low normal B12 levels are common and may be associated with depression and the inadequate response to antidepressant treatment in patients with depression [14]. Vitamin B12 supplementation with antidepressants has significantly improved depressive symptoms in our group. Larger, multi-center studies are required to extend and replicate our findings. There are several strategies for treating depression. Depending upon each individual's characteristics and symptoms, healthcare professionals may employ one or more types of psychotherapy that rely upon a sequence of interpersonal treatment sessions with a trained professional. In addition, clinicians may suggest that a patient try one of a number of different medications. Lifestyle changes, including improvements in sleeping and eating habits, physical activity and stress reduction have also proven very helpful in managing symptoms. Neuropsychiatric manifestations such as memory loss, depression, hypomania, paranoid psychosis with auditory and visual hallucinations the so called megaloblastic madness have been described with vitamin B-12 deficiency. Patients may present with violent behavior or more subtle personality changes. They may also present with vague complaints typical of aging such as fatigue, generalized weakness and loss of memory. Cognitive testing may reveal frank dementia. These complaints may be attributed to aging or psychiatric illness unless a high index of suspicion is entertained and a test for vitamin B-12 deficiency is carried out. It is still not clear if mild or moderate B12 deficiency can cause dementia and whether supplementation of the diet with B12 can prevent or delay the onset of dementias like Alzheimer's disease. Patients who are demented usually show little to no cognitive improvement with B12 supplementation.

REFERENCES

1. Murray, C. J., Lopez, A. D., & World Health Organization. (1996). The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary.
2. Mirza, I., & Jenkins, R. (2004). Risk factors, prevalence, and treatment of anxiety and depressive disorders in Pakistan: systematic review. *Bmj*, *328*(7443), 794-798.
3. Gelenberg, A. J., Freeman, M. P., Markowitz, J. C., Rosenbaum, J. F., Thase, M. E., Trivedi, M. H., ... & Schneck, C. D. (2010). Practice guideline for the treatment of patients with major depressive disorder third edition. *The American journal of psychiatry*, *167*(10), 1.
4. Thase, M. E., Entsuah, A. R., & Rudolph, R. L. (2001). Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *The British journal of psychiatry*, *178*(3), 234-241.
5. Puech, A., Montgomery, S. A., Prost, J. F., Solles, A., & Briley, M. (1997). Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability.
6. Antai-Otong, D. (2007). The Art of Prescribing: Monotherapy Antidepressant: A Thing of the Past? Implications for the Treatment of Major Depressive Disorder. *Perspectives in psychiatric care*, *43*(3), 142-145.
7. Shah, R. A., Qureshi, M. B., & Khan, A. A. (2005). Magnitude of vitamin A deficiency in poor communities of the four selected districts of Punjab

using-(rapid assessment technique). *Annals of King Edward Medical University*, *11*(3), 314-318.

8. Khan, R. M., & Iqbal, M. P. (2006). Deficiency of vitamin C in South Asia. *Pakistan Journal of Medical Sciences*, *22*(3), 347-355.
9. Hashim, H., & Tahir, F. (2006). frequency of vitamin B12 and folic acid deficiencies among patients of megaloblastic anemia. *Ann pakinst Med Sci*, *2*, 192-194.
10. Yajnik, C., Deshpande, S. S., Lubree, H. G., Naik, S. S., Bhat, D. S., Uradey, B. S., ... & Yudkin, J. S. (2006). Vitamin B12 deficiency and hyperhomocysteinemia in rural and urban Indians. *Japi*, *54*(775), 82.
11. Fakhrzadeh, H., Ghotbi, S., Pourebrahim, R., Nouri, M., Heshmat, R., Bandarian, F., ... & Larijani, B. (2006). Total plasma homocysteine, folate, and vitamin b12 status in healthy Iranian adults: the Tehran homocysteine survey (2003–2004)/a cross–sectional population based study. *BMC public health*, *6*(1), 29.
12. Syed, E. U., Wasay, M., & Awan, S. (2013). Vitamin B12 supplementation in treating major depressive disorder: a randomized controlled trial. *The open neurology journal*, *7*, 44.
13. Lim, H. S., & Heo, Y. R. (2002). Plasma total homocysteine, folate, and vitamin B12 status in Korean adults. *Journal of nutritional science and vitaminology*, *48*(4), 290-297.
14. Refsum, H., Yajnik, C. S., Gadkari, M., Schneede, J., Vollset, S. E., Örning, L., ... & Ueland, P. M. (2001). Hyperhomocysteinemia and elevated methylmalonic acid indicate a high prevalence of cobalamin deficiency in Asian Indians. *The American journal of clinical nutrition*, *74*(2), 233-241.