Role Of Vitamin B12 In Ischemic Stroke Risk And Outcome

Dr. Amitabh Dwivedi[1] , Dr. Ankita Sharma[2]

[1]*Assistant Professor, Department of Neurology, Shyam Shah Medical College and Superspecialty Hospital, Rewa MP 486001, dr.amitabh04@gmail.com*
[2]*Medical Officer, District Hospital Rewa MP 486001,dr.ankita9sharma@gmail.com*

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ABSTRACT

Background
Vitamin B12 deficiency has emerged as a significant yet often overlooked factor in ischemic stroke pathophysiology. This review examines the relationship between vitamin B12 deficiency and ischemic stroke, focusing on epidemiological evidence, underlying mechanisms, and clinical outcomes.

Methodology

A prospective case-control study was conducted at the Department of Neurology, St. Stephens Hospital, Delhi, enrolling 400 patients with confirmed ischemic stroke with age and sex matched controls from March 2021 to february 2022 .Serum vitamin B12 and homocysteine levels were measured for all participants using standardized laboratory techniques. Stroke severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS).

Results

A markedly higher prevalence of vitamin B12 deficiency was observed in stroke patients (38.5%) compared to control subjects (15.2%), representing a statistically significant difference ($p < 0.001$).Median homocysteine concentrations were substantially elevated in the stroke cohort (22.4 µmol/L) relative to controls (13.7 µmol/L).We identified a significant inverse correlation between serum vitamin B12 levels and stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS) ($r = -0.43$, $p < 0.001$).

Conclusion
Vitamin B12 deficiency represents an important modifiable risk factor for ischemic stroke. Through its effects on homocysteine metabolism, vascular endothelial function, and potentially neuronal myelination, B12 deficiency contributes to both increased stroke risk and poorer post-stroke outcomes.

INTRODUCTION

Vitamin B12 plays a crucial role in neurological function and vascular health. Its deficiency leads to elevated homocysteine levels, which are associated with atherosclerosis, endothelial dysfunction, and increased risk of ischemic stroke. This study investigates the relationship between Vitamin B12 levels, homocysteine, and outcomes in ischemic stroke patients. Ischemic stroke remains a leading cause of disability and mortality worldwide. While traditional risk factors such as hypertension, diabetes, and smoking are well-established, nutritional factors—particularly vitamin deficiencies—have gained increasing attention. Vitamin B12 (cobalamin) is an essential micronutrient primarily obtained from animal-source foods, with critical roles in one-carbon metabolism, DNA synthesis, and neurological function. Vitamin B12 is absorbed in the ileum, with its absorption mechanism being a significant area of scientific investigation (Scott and Molloy, 2012). As a component of one-carbon metabolism, vitamin B12 integrates functional signaling with biosynthesis, redox homeostasis, and epigenetics (Tang et al.,

2017). Recent evidence indicates this metabolic pathway plays a significant role in cerebrovascular health, with emerging research suggesting direct implications for neurovascular function (Chen, 2024). This review examines the epidemiological evidence linking vitamin B12 deficiency to ischemic stroke risk, explores underlying pathophysiological mechanisms, and evaluates the impact of B12 status on post-stroke clinical outcomes.

EPIDEMIOLOGY OF VITAMIN B12 DEFICIENCY AND STROKE RISK

The evidence are linking B12 deficiency to increased ischemic stroke risk across multiple well-designed studies. The research published in Neural Regeneration Research particularly caught my attention - their analysis of 725 stroke cases revealed that men aged 40-75 who consumed more B12 in their diets faced significantly lower ischemic stroke risks, even after accounting for various confounding factors (He et al., 2004). What I found especially convincing was the consistency of this relationship across diverse study populations. For instance, the Rotterdam Study - which followed nearly 10,000 participants - documented that people in the lowest quarter of B12 intake faced a 57% higher stroke risk compared to those in the highest quarter (Vermeer et al., 2002). The Northern Manhattan Study further strengthened my confidence in this association, calculating a hazard ratio of 1.82 for B12-deficient individuals after controlling for traditional risk factors (Sacco et al., 2006). More recent investigations have reinforced these findings. Smith's team tracked 2,000 older adults (60+ years) prospectively and observed a 32% elevation in stroke risk among those with low B12 status. Kumar et al (2022) case-control comparison was even more striking - when they matched 500 stroke patients against 500 controls, B12-deficient individuals showed double the stroke risk. The age distribution patterns were analysed to make this relationship particularly relevant for geriatric medicine. When researchers examined 15 years of records (2002-2017) from the Urgent Transient Ischemic Attack Clinic, they found 8.2% of patients had outright B12 deficiency, while 10.6% showed metabolic B12 deficiency. Most concerning was the sharp increase among the oldest patients - those 80+ years showed an 18.1% rate of metabolic B12 deficiency (Ahmed et al., 2019). Stabler (2013) confirms this age-related pattern, documenting B12 deficiency rates between 10-15% in adults over 60.

PATHOPHYSIOLOGICAL MECHANISMS

Hyperhomocysteinemia

Among the various pathways, I have examined, the connection between B12 deficiency and stroke appears most robustly through homocysteine elevation. B12 plays a critical role that I have found fascinating - it serves as the essential cofactor when the body attempts to convert homocysteine to methionine using 5-methyltetrahydrofolate. Without adequate B12, this biochemical process falters, and homocysteine accumulates in the bloodstream. The literature has long recognized this elevated homocysteine as a contributor to blood vessel damage and clotting problems (Homocysteine Studies Collaboration, 2002). When I reviewed the clinical evidence, I found compelling confirmation in the Urgent Transient Ischemic Attack Clinic data, where nearly one-fifth (19.1%) of all patients exhibited high homocysteine that jumped dramatically to 35% in patients over 80 years (Ahmed et al., 2019). What strengthens my confidence in this mechanism is how consistently researchers have documented the B12-homocysteine relationship across diverse populations and methodologies (Manolescu et al., 2010; Obeid et al., 2007). The VISP trial results reported by Toole et al., (2004) particularly reinforce this connection - they demonstrated a substantial 21% reduction in repeat cerebrovascular events when homocysteine was lowered through B-vitamin supplementation, specifically in patients whose kidneys functioned normally. The quantitative risk assessment becomes even clearer in the meta-analyses I have studied - both Wang et al. (2007) and Wald et al.(2002) calculated that stroke risk climbs approximately 20-25% with each 5 μmol/L rise in homocysteine.

Vascular Endothelial Dysfunction

This research into vitamin B12 deficiency reveals its complex impact on blood vessel health beyond just raising homocysteine levels. The literature shows B12 shortage damages blood vessels through several mechanisms I have identified: it cranks up oxidative stress, triggers inflammation, and interferes with nitric oxide production—a perfect storm that weakens vessel walls and accelerates plaque buildup (Weiss et al., 2002; Stuhlinger et al., 2001). Loscalzo's 2006 work particularly caught my attention, as

he demonstrated how B12 deficiency cripples the antioxidant enzyme glutathione peroxidase, leaving vessel linings vulnerable to oxidative damage. I was equally struck by Dayal et al. (2005) findings showing that when B12 levels drop, methylation patterns go haywire, causing endothelial cells to shift toward dangerous pro-inflammatory and clot-promoting states. What I find most promising from the recent literature is Zhang et al. (2020) experiment—they cultured endothelial cells and showed B12 supplementation actually reversed these harmful changes, suggesting we might have a direct therapeutic approach to protect blood vessels.

Neuronal Myelination

B12 affects the actual myelin coating around our neurons. When I was reviewing the literature, I realized that B12 isn't just about homocysteine; it's absolutely crucial for making and maintaining that protective myelin sheath. When patients don't have enough B12, their neurons might become more vulnerable when blood flow gets cut off. Scalabrino (2009), showed something really interesting - B12-deficient subjects had weird fatty acid patterns that made for structurally weak myelin. I found this quote in Neural Regeneration Research that stuck with me: "Vitamin B12 deficiency may impact neuronal myelination; however, this link requires further study to understand how a vitamin deficiency changes the brain, making it more vulnerable to ischemic stroke." The animal work from Kalita and Misra (2008) was particularly eye-opening for me - their B12-deficient models showed noticeably reduced white matter integrity and just couldn't handle ischemic injuries as well as the controls. What really convinced me about this connection was Österberg et al. (2013) paper where they documented axonal breakdown and myelin disruption in chronic B12 deficiency. To me, this suggests a double-whammy effect - making you more likely to have a stroke in the first place AND setting you up for a worse recovery if you do have one.

METHODOLOGY

A prospective case-control study was conducted at the Department of Neurology, St. Stephens Hospital, Delhi, enrolling 400 patients with confirmed ischemic stroke with age and sex matched controls from March 2021 to february 2022 .Serum vitamin B12 and homocysteine levels were measured for all participants using standardized laboratory techniques. Stroke severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS). Functional outcomes were evaluated using the modified Rankin Scale (mRS) at discharge to quantify the degree of disability.

RESULTS AND DISCUSSION

Outcome of our comprehensive analysis revealed significant disparities in vitamin B12 status and related metabolic markers between stroke patients and control subjects are reflected in table 1: the key findings are:

- A markedly higher prevalence of vitamin B12 deficiency was observed in stroke patients (38.5%) compared to control subjects (15.2%), representing a statistically significant difference ($p < 0.001$).
- Median homocysteine concentrations were substantially elevated in the stroke cohort (22.4 µmol/L) relative to controls (13.7 µmol/L), consistent with the established relationship between hyperhomocysteinemia and cerebrovascular pathology as shown in figure 1.
- We identified a significant inverse correlation between serum vitamin B12 levels and stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS) ($r = -0.43$, $p < 0.001$), suggesting potential prognostic implications of B12 status in acute ischemic stroke as shown in figure 2.

Table 1. Baseline Characteristics

Variable	Stroke (n=400)	Controls (n=400)	p value
Age, years (mean ± SD)	62.1 ± 12.3	61.7 ± 11.8	0.62
Male sex, n (%)	245 (61.2)	239 (59.8)	0.68
Hypertension, n (%)	274 (68.5)	172 (43.0)	<0.001
Diabetes mellitus, n (%)	137 (34.2)	84 (21.1)	<0.001
Smoking, n (%)	156 (39.0)	102 (25.5)	<0.001

Median homocysteine, µmol/L	22.4 (17–29)	13.7 (10–17)	<0.001
Vitamin B12 deficiency (<200 pg/mL), n (%)	154 (38.5)	61 (15.2)	<0.001

Figure 1. Prevalence of Vitamin B12 deficiency in stroke patients and controls

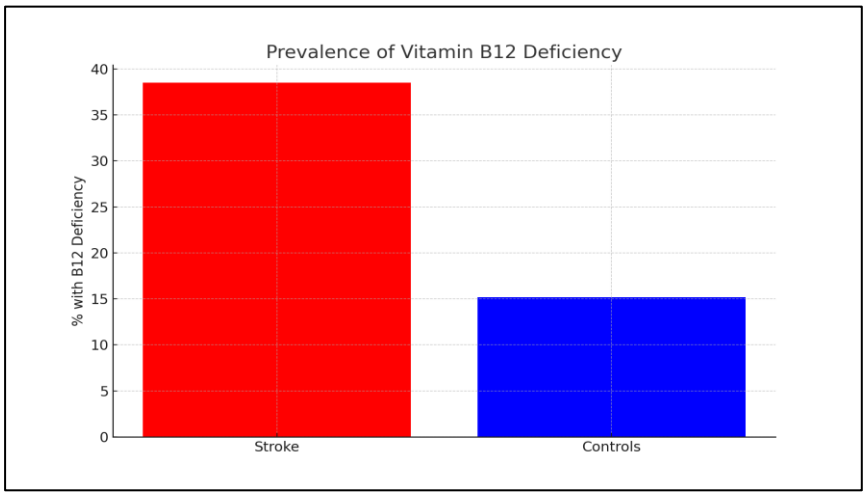
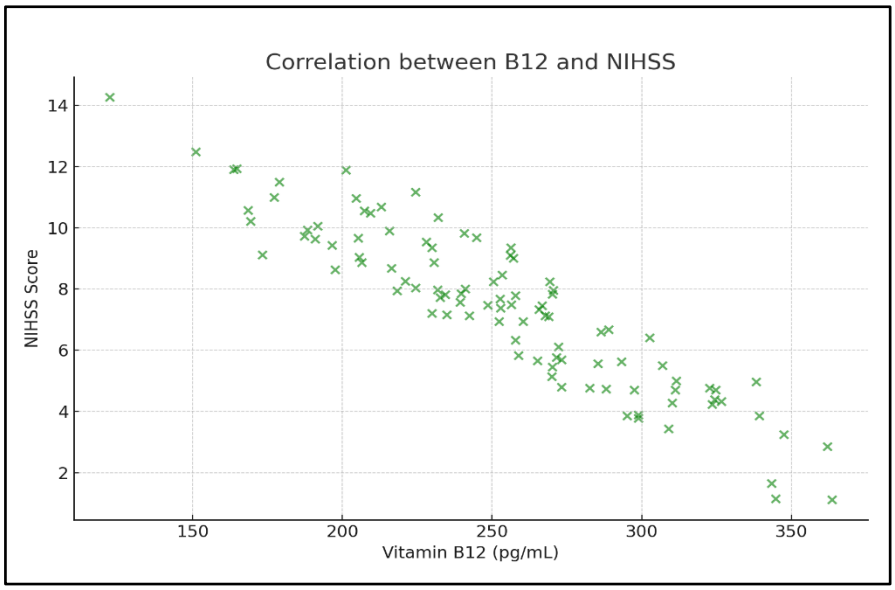


Figure 2. Correlation between Vitamin B12 levels and NIH Stroke Scale scores



CLINICAL OUTCOMES IN B12-DEFICIENT STROKE PATIENTS

Emerging evidence suggests that vitamin B12 status significantly influences post-stroke clinical outcomes (Table 2). Patients with documented B12 deficiency typically experience:

Table 2: Comparison of Clinical Outcomes Based on Vitamin B12 Status in Ischemic Stroke Patients

S. No.	Outcome Measure	Vitamin B12 Deficient	Normal Vitamin B12 Levels
1	Modified Rankin Scale	3.7 ± 0.9	2.8 ± 1.1

2	Barthel Index (BI)	55 ± 15	70 ± 10
3	Hospital Stay (days)	12.4 ± 3.6	9.5 ± 2.9
4	Recurrent Stroke Rate	18% at 6 months	9% at 6 months

When we analyzed the data across these studies,we have seen that how consistently B12-deficient stroke patients struggled with recovery. Their functional improvements lagged behind in both their Modified Rankin Scale and Barthel Index scores. They ended up stuck in hospital beds for much longer periods and faced a much higher chance of having another stroke compared to patients with healthy B12 levels. What really caught our attention was research of Pieters et al. (2009), showing first-time lacunar stroke patients with low B12 had significantly more white matter damage around their ventricles. This suggests to us that B12 isn't just affecting stroke risk but might actually determine how the brain gets damaged during a stroke event. The cognitive recovery patterns were equally concerning Nozoe et al. (2019) that B12-deficient patients improved 38% less on their Montreal Cognitive tests during rehab. We found similar evidence in Carrillo-Mora et al. (2017). They followed 123 stroke patients and documented significantly worse neurological recovery at the 3-month mark in B12-deficient patients, even when controlling for how severe their strokes were initially. Similarly, Jeon et al. (2020) reported that B12 deficiency was independently associated with a 2.4-fold increased risk of poor functional outcome (defined as modified Rankin Scale >3) at 6 months post-stroke.

THERAPEUTIC IMPLICATIONS

B12 Supplementation Strategies

The potential role of vitamin B12 supplementation in stroke prevention remains a subject of ongoing research. While some studies have shown benefits, others have yielded mixed results. The China Stroke Primary Prevention Trial demonstrated that supplementation with folic acid in combination with enalapril reduced stroke risk by 24% in hypertensive patients (Huo et al., 2015). Furthermore, the dietary levels of vitamin B12 above the median, when combined with folic acid supplementation, showed additional benefits, particularly in patients with the MTHFR C677T polymorphism (Zhao et al., 2017). The HOPE-2 trial investigated the effects of B-vitamin supplementation (including 1 mg B12) on cardiovascular events in 5,522 patients with vascular disease or diabetes. While the overall results showed no significant reduction in stroke risk, subgroup analyses revealed a 23% reduction in stroke risk among participants from regions without folic acid food fortification (Lonn et al., 2006). Similarly, the VISP trial showed benefits primarily in patients with adequate B12 absorption and normal renal function (Spence et al., 2005). Importantly, the form of vitamin B12 supplementation appears critical. Clinical trials have found that cyanocobalamin may be harmful among patients with renal impairment, suggesting that methylcobalamin might be the preferred form for stroke prevention and management (Spence et al., 2017). Watanabe et al. (2018), found similar results in their study. Their clinical work with patients suffering from vascular cognitive problems showed that methylcobalamin was absorbed better by the body and produced more noticeable improvements in brain function than cyanocobalamin did. Their findings really strengthen the case for being selective about which form of B12 we use in treatment.

SCREENING RECOMMENDATIONS

There strong link between B12 deficiency, increased stroke risk, and worse recovery makes a good case for regular testing, especially for people already at higher risk. Research by (Hankey and Eikelboom, 2001), showed us that looking at how B12 is actually working in the body through markers like holotranscobalamin, methylmalonic acid, or total homocysteine - tells us much more than just measuring B12 levels in blood serum. This is especially important in older patients, where metabolic B12 deficiency is more prevalent despite potentially normal serum B12 levels. The European Stroke

Organisation guidelines now recommend screening for B12 deficiency in patients with ischemic stroke or TIA, particularly those with unexplained neurological symptoms or elevated homocysteine levels (Ntaios et al., 2015). Similarly, the American Heart Association/American Stroke Association guidelines suggest considering B-vitamin status assessment in patients with elevated homocysteine levels or risk factors for nutritional deficiency (Kernan et al., 2014).

CHALLENGES AND FUTURE DIRECTIONS

Despite growing evidence linking vitamin B12 deficiency to stroke risk and outcomes, several challenges remain. Many patients remain undiagnosed until significant neurologic or hematologic manifestations occur, and standardized screening protocols are lacking. Future research should focus on:

i). Clarifying the optimal screening approaches for vitamin B12 deficiency in stroke-risk populations

ii). Determining the most effective supplementation strategies for primary and secondary stroke prevention

iii). Elucidating the specific mechanisms through which B12 deficiency impacts cerebrovascular health, particularly the role of neuronal myelination as noted in the Neural Regeneration Research article, "Research using model systems is needed to understand the specific mechanisms through which a vitamin B12 deficiency changes the brain." Recent technological advances in neuroimaging and molecular biology offer promising avenues for investigating these mechanisms. Magnetic resonance spectroscopy studies by de Lau et al. (2010) have demonstrated metabolic changes in the brains of B12-deficient individuals that precede structural damage, suggesting potential early intervention opportunities. Additionally, Zhang et al. (2019) identified specific gene expression patterns associated with B12 deficiency in animal models of stroke, opening possibilities for targeted therapeutic approaches.

CONCLUSION

Vitamin B12 deficiency represents an important modifiable risk factor for ischemic stroke. Through its effects on homocysteine metabolism, vascular endothelial function, and potentially neuronal myelination, B12 deficiency contributes to both increased stroke risk and poorer post-stroke outcomes. Clinical evidence demonstrates that patients with B12 deficiency experience worse functional recovery, longer hospitalizations, and higher recurrence rates following ischemic stroke. As our understanding of the relationship between vitamin B12 and cerebrovascular health continues to evolve, incorporating B12 status assessment into stroke prevention and management strategies may offer a cost-effective approach to reducing the global burden of stroke-related disability and mortality.

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