RESEARCH PAPER

Impact of Proton Pump Inhibitor Therapy on Micronutrient and Cognitive Function in Gastroesophageal Reflux Disease Patients: A Prospective Study

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are among most frequently prescribed treatments for gastroesophageal reflux disease (GERD) around the world. However, cognitive function alterations associated with proton pump inhibitor use and the underlying mechanisms, including the potential role of changes in micronutrient levels, are still not well understood. **Objective:** Assessing cognitive performance change along with serum Vitamin B12, Magnesium, Zinc, Iron, and Vitamin D3 after two-month of Esomeprazole or Dexlansoprazole treatment using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) for cognitive testing. **Methods:** A prospective cohort study carried out at PAR Private Hospital, Erbil, Kurdistan Region of Iraq through the period from April 2025 to February 2026. Enrolling Sixty patients with recent gastroesophageal reflux disease diagnosis and prescribed PPI medication for two months as the following: 22 received Esomeprazole 40 mg once daily and 38 received Dexlansoprazole 30 mg twice daily for two months. Serum micronutrient levels and cognitive scores were measured at baseline and after two months of therapy. The Wilcoxon signed-rank test was used for within-group comparisons due to non-normal data distribution. **Results:** Significant post-treatment reductions were observed in serum Vitamin B12 (P=0.007), Magnesium (P=0.044), Zinc (P=0.005), and Iron (P=0.033). Vitamin D3 increased non-significantly (P=0.485). MMSE was unchanged (P=0.526) while MoCA declined significantly (P=0.004). No significant between-drug difference was found for any parameter. Vitamin B12 and Iron correlated selectively with MoCA scores. **Conclusion:**Two months of PPI therapy significantly depleted Vitamin B12, Magnesium, Zinc, and Iron, and produced a cognitive decline detectable by MoCA but not MMSE. Both drugs produced equivalent effects. MoCA is more sensitive than MMSE for detecting mild PPI-associated cognitive change, with Vitamin B12 and Iron as the principal nutritional correlates.

Keywords: Cognitive function, GERD, Micronutrients, MoCA, Proton pump inhibitors
How to site this article: Leyan Safaa Salih, Kawa Fareq Dizaye, "Impact of Proton Pump Inhibitor Therapy on Micronutrient and Cognitive Function in Gastroesophageal Reflux Disease Patients: A Prospective Study" Int J Drug Deliv Technol. 2026;16(80s): 800-809; DOI: 10.25258/ijddt.16.80s.94

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a persistent digestive condition featured with the pathological movement of stomach contents into the oesophagus, causing mucosal damage and disturbing symptoms. Its development involves dysfunction of the oesophagogastric junction, in addition to other factors like with acid load, mucosal defence, and visceral hypersensitivity[1,2]. Frequently appearing predisposing factors were include excess body weight, smoking, and genetic susceptibility.[2].

Proton pump inhibitors (PPIs) have become the dominant pharmacological treatment for acid-related disorders and are among the highest-volume prescriptions worldwide[3,4]. These agents form a covalent bond with the H^+/K^--ATPase on the luminal surface of parietal cells, permanently blocking the terminal step of gastric acid secretion explaining the more complete acid suppression it achieve compared to histamine-2 receptor antagonists that are vulnerable to partial bypassing with alternative pathways [5].

Despite their effectiveness, long-term PPI use has been associated with enteric infections, gut microbiome disruption, bone loss, and kidney disease[6,7]. Evidence also links PPI use to cognitive deterioration: German longitudinal ageing data showed higher dementia incidence in chronic PPI users[8], and three of four major European observational analyses reported an approximately 1.4-fold elevated dementia risk[9].

A proposed mechanism linking PPI use to cognitive change is the depletion of micronutrients with established neurobiological roles. By suppressing gastric acid, PPIs impair the absorption of Vitamin B12, Magnesium, Zinc, Iron, and Vitamin D3[4,5]. Vitamin B12 deficiency disrupts both homocysteine metabolism — elevating a neurotoxin that promotes neuroinflammation and hippocampal atrophy[8] — and SAM-dependent methylation essential for myelin

integrity and neurotransmitter synthesis; both pathways converge to produce cognitive decline[10]. Iron deficiency impairs dopamine and serotonin synthesis and reduces mitochondrial neuronal energy production[11]. Magnesium deficiency promotes excitotoxicity through NMDA receptor dysregulation and neuroinflammatory pathways linked to neurodegeneration and cognitive decline[12]. Zinc, one of the most abundant metal ions in the central nervous system, regulates synaptic transmission, neuroplasticity, and antioxidant defence; its deficiency is associated with cognitive impairment and increased dementia risk[13]. Vitamin D3 receptors are widely expressed in the human brain, and higher brain 25-hydroxyvitamin D3 concentrations have been associated with 25–33% lower odds of dementia or mild cognitive impairment[14].

Short-term testing with the Cambridge Neuropsychological Test Automated Battery (CANTAB) showed that Esomeprazole over seven days impaired sustained attention, spatial working memory, and executive planning[15]. Dexlansoprazole was linked to a significant increase in dementia risk in a longitudinal study tracking multiple PPIs over 18 months[16]. Most available studies have used administrative databases, neuroimaging, or specialist testing platforms rather than practical bedside screening tools validated for early cognitive change.

In this study , dexlansoprazole and esmoprazole are both included from the same therapeutical group of medications. However, the major difference between them is the better 24 hours acid suppression coverage by dexlansoprazole compared to esmoprazole mainly due to its dual-delayed release formulatione[17]. Studies concerned with short term effect of PPI and comparing these two specific agents are still limited. This study main aim is to test the short term PPI therapy effect on cognition and if it was related to micronutrients levels alterations (serum Vitamin B12, Magnesium, Zinc, Iron, and Vitamin D3) , detected by biological blood tests for the micronutrients and cognition assessments using the widely used MMSE neurological test and the more sensitive MoCA test. To our knowledge, this is the first prospective study to apply both cognitive tests at two time points before-and-after to measure the cognitive impact of PPI therapy.

MATERIALS AND METHODS

Patients and study design

A prospective cohort study was carried out through the period April 2025 and February 2026 at PAR Private Hospital, Erbil, Kurdistan Region of Iraq. Patients aging between 18 to 70 who have been recently diagnosed with gastroesophageal reflux disease were enrolled after matching the study eligibility criteria especially intact cognition level when enrolled. Any patients with history of cognitive impairment; recent PPI treatment for two or more months; diabetes mellitus; hypothyroidism; pregnancy; and use of combined oral contraceptive pills were excluded from the study. Sixty patients who completed the two-month follow-up were included in the final analysis. Those 60 patients came back as the following: 22 received Esomeprazole 40 mg once daily and 38 received Dexlansoprazole 30 mg twice daily, as prescribed by their gastroenterologist. Ethical approval was obtained from the Scientific Committee of the College of Medicine, Hawler Medical University, and the Ethical Committee of the General Directorate of Health in Erbil. Verbal informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and adhered to STROBE reporting guidelines.

Laboratory methods

Peripheral venous blood (3 mL) was collected into plain tubes at baseline following cognitive assessment. Blood was allowed to clot at room temperature for 30 minutes, centrifuged at 2500 rpm for 10 minutes, and serum was stored at −40°C until batch analysis; identical collections were made at two-month follow-up. Serum Vitamin B12 was measured by electrochemiluminescence immunoassay (ECLIA) on a Roche Diagnostics COBAS analyser (Elecsys Vitamin B12 II; REF 07212771 190; Roche Diagnostics GmbH, Mannheim, Germany)[18]. Serum 25-hydroxyvitamin D3 was measured by ECLIA (Elecsys Vitamin D; REF 06506780 160; Roche Diagnostics GmbH)[18]. Serum Iron was quantified by FerroZine photometric colorimetric method (IRON2 Iron Gen.2; REF 10059605 500; Roche Diagnostics GmbH)[18]. Serum Magnesium was measured by xylidyl blue colorimetric endpoint method (MG2 Magnesium Gen.2; REF 06481647 500; Roche Diagnostics GmbH)[18]. Serum Zinc was measured by colorimetric assay (Liofilchem S.r.l., Roseto degli Abruzzi, Italy). Cognitive function was assessed at baseline and at two-month follow-up by the same certified examiner. The MMSE is a 30-point validated screening tool assessing orientation, registration, attention, recall, and language. The MoCA is a 30-point tool developed specifically to detect mild cognitive impairment, covering visuospatial-executive function, naming, attention, language, abstraction, and delayed recall; one additional point is awarded for patients with 12 or fewer years of formal education[19]. Both tools define normal cognition as 26/30 or above. The MoCA examiner completed the official certification program.

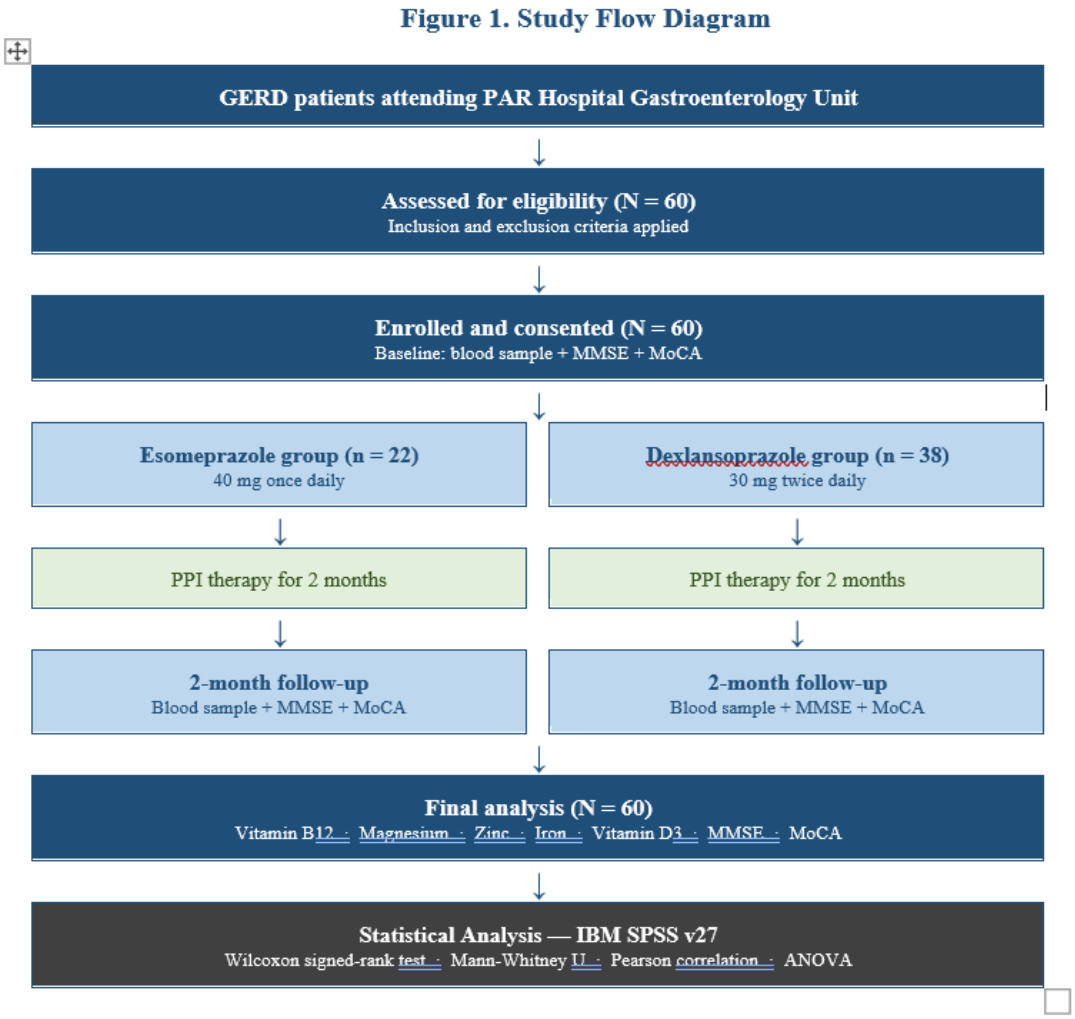

Figure 1. Study flow diagram showing patient enrolment, drug group allocation, two-month follow-up, and analysis.

Statistical analysis

Data were analysed using IBM SPSS Statistics version 27. The Shapiro-Wilk test confirmed non-normal distribution; therefore non-parametric tests were used throughout. Within-group pre- and post-treatment comparisons used the Wilcoxon signed-rank test. Between-group comparisons used the Mann-Whitney U test for continuous variables and chi-square for categorical variables. Pearson correlation coefficients were calculated for same-timepoint micronutrient-cognitive pairs. Partial correlation analysis controlled for educational level in the age-cognition analysis. Educational subgroup differences were examined by one-way ANOVA with post-hoc testing; subgroup pairs sharing the same lower-case letter (a, b) do not differ significantly at α=0.05. Statistical significance was set at $P<0.05$ (two-tailed) and exact P values are reported throughout.

RESULTS

Patient characteristics

The study enrolled 60 newly diagnosed GERD patients. Mean age was 41.23±13.44 years (range 18–70); 36 (60.0%) were female and 24 (40.0%) male. Twenty-two (36.7%) received Esomeprazole and 38 (63.3%) received Dexlansoprazole. Educational distribution: uneducated 5 (8.3%), primary 13 (21.7%), secondary 7 (11.7%), institute diploma 10 (16.7%), and university degree or above 25 (41.7%). The two drug groups did not differ significantly at baseline in sex (P=0.913), educational level (P=0.268), or any measured vitamin, mineral, or cognitive score (all P>0.05).

Effect of PPI treatment on micronutrients and cognitive scores

After two months of PPI therapy, serum Vitamin B12 (P=0.007), Magnesium (P=0.044), Zinc (P=0.005), and Iron (P=0.033) all fell significantly. Vitamin D3 rose non-significantly (P=0.485). MMSE was unchanged (P=0.526). MoCA declined significantly (P=0.004). Full data are in Table 1.

Table 1. Vitamins, minerals and cognitive scores before and after PPI treatment, all patients (N=60)

Parameter	Before treatment Mean ± SD	After treatment Mean ± SD	P-value
Vitamin B12 (pg/mL)	373.87 ± 116.37	321.32 ± 108.44	0.007*
Magnesium (mmol/L)	2.1195 ± 0.41478	1.9592 ± 0.34054	0.044*
Zinc (µg/dL)	69.2562 ± 33.998	52.4430 ± 25.429	0.005*
Iron (µg/dL)	70.2328 ± 33.054	57.4870 ± 28.532	0.033*
Vitamin D3 (ng/mL)	24.6342 ± 14.161	26.560 ± 13.854	0.485
MMSE (score)	28.85 ± 1.071	28.73 ± 1.103	0.526
MoCA (score)	28.18 ± 1.432	27.53 ± 1.641	0.004*

*P<0.05 (Wilcoxon signed-rank test). Values are Mean±SD.

Of all patients, 76.7% had a stable MMSE score while 63.3% showed a declining MoCA score (Table 2).

Table 2. Direction of change in MMSE and MoCA scores after PPI treatment (N=60)

Cognitive test	No change n (%)	Decrease n (%)	Increase n (%)	P-value
MMSE	46 (76.7)	11 (18.3)	3 (5.0)	0.001
MoCA	16 (26.7)	38 (63.3)	6 (10.0)	0.001

Effect of PPI treatment by drug group

Both Esomeprazole and Dexlansoprazole independently produced significant reductions in Vitamin B12, Zinc, Iron, and MoCA score (Tables 3 and 4). MMSE was unchanged with either drug. Vitamin D3 did not reach significance in either group. Magnesium fell significantly only in the Dexlansoprazole group (P=0.043), not in the Esomeprazole group (P=0.133). Direct comparison of the magnitude of change showed no significant between-drug difference for any parameter, including Magnesium (mean change −0.128 vs −0.132 mmol/L; P=0.818), confirming equivalent short-term effects (Table 5).

Table 3. Vitamins, minerals and cognitive scores before and after treatment — Esomeprazole group (n=22)

Parameter	Before Mean ± SD	After Mean ± SD	P-value
Vitamin B12 (pg/mL)	383.46 ± 98.92	315.23 ± 88.53	0.001*
Magnesium (mmol/L)	2.095 ± 0.416	1.967 ± 0.419	0.133
Zinc (µg/dL)	62.36 ± 20.15	46.02 ± 21.47	<0.001*
Iron (µg/dL)	70.92 ± 32.22	53.07 ± 27.04	0.005*
Vitamin D3 (ng/mL)	25.15 ± 11.53	25.08 ± 11.94	0.973
MMSE (score)	28.86 ± 0.94	28.68 ± 0.84	0.213
MoCA (score)	28.00 ± 1.88	27.23 ± 2.05	<0.001*

*P<0.05 (Wilcoxon signed-rank test). Values are Mean±SD.

Table 4. Vitamins, minerals and cognitive scores before and after treatment — Dexlansoprazole group (n=38)

Parameter	Before Mean ± SD	After Mean ± SD	P-value
Vitamin B12 (pg/mL)	368.32 ± 126.31	324.84 ± 119.45	0.009*
Magnesium (mmol/L)	2.134 ± 0.419	1.955 ± 0.292	0.043*
Zinc (µg/dL)	73.25 ± 39.60	56.16 ± 27.03	0.005*
Iron (µg/dL)	69.84 ± 33.95	60.04 ± 29.41	0.028*
Vitamin D3 (ng/mL)	24.34 ± 15.62	27.42 ± 14.93	0.061
MMSE (score)	28.84 ± 1.15	28.76 ± 1.24	0.262
MoCA (score)	28.29 ± 1.11	27.71 ± 1.35	<0.001*

*P<0.05 (Wilcoxon signed-rank test). Values are Mean±SD.

Table 5. Mean change (after minus before) compared between drug groups

Parameter	Esomeprazole (n=22) Mean ± SD	Dexlansoprazole (n=38) Mean ± SD	P-value
Vitamin B12 (pg/mL)	-68.23 ± 81.33	-43.47 ± 96.82	0.217
Magnesium (mmol/L)	-0.128 ± 0.385	-0.132 ± 0.499	0.818

Zinc (µg/dL)	-16.34 ± 18.29	-17.09 ± 34.86	0.736
Iron (µg/dL)	-17.85 ± 26.37	-9.79 ± 26.35	0.258
Vitamin D3 (ng/mL)	-0.160 ± 8.43	3.081 ± 9.84	0.201
MMSE (score)	-0.18 ± 0.66	-0.08 ± 0.43	0.231
MoCA (score)	-0.77 ± 0.53	-0.58 ± 0.76	0.394

Values are Mean±SD. Between-group comparisons by Mann-Whitney U test. All P>0.05.

Pearson correlation analysis

Pearson analysis identified significant same-timepoint correlations (Table 6). Age correlated negatively with MMSE before (r=−0.295, P=0.022) and after treatment (r=−0.308, P=0.017) but not with MoCA. Vitamin B12 before treatment correlated with MMSE before treatment (r=0.274, P=0.034; Figure 2). Vitamin B12 after treatment correlated with MoCA after treatment (r=0.337, P=0.009; Figure 3). Iron correlated with MoCA before (r=0.280, P=0.030; Figure 4) and after treatment (r=0.275, P=0.033; Figure 5), without association with MMSE. Post-treatment Zinc correlated significantly with post-treatment Vitamin B12 (r=0.267, P=0.039), Iron (r=0.375, P=0.003), Vitamin D3 (r=0.335, P=0.009), and Magnesium (r=0.358, P=0.005). Zinc, Magnesium, and Vitamin D3 showed no significant correlation with any cognitive score.

Table 6. Statistically significant Pearson correlations (N=60)

Correlation	r	P-value
Age vs MMSE before treatment	−0.295	0.022
Age vs MMSE after treatment	−0.308	0.017
Vitamin B12 before vs MMSE before	0.274	0.034
Vitamin B12 after vs MoCA after	0.337	0.009
Iron before vs MoCA before	0.280	0.030
Iron after vs MoCA after	0.275	0.033
Magnesium before vs Zinc before	0.264	0.042
Magnesium after vs Zinc after	0.358	0.005
Zinc after vs Iron after	0.375	0.003
Zinc after vs Vitamin B12 after	0.267	0.039
Zinc after vs Vitamin D3 after	0.335	0.009

Same-timepoint correlations only.

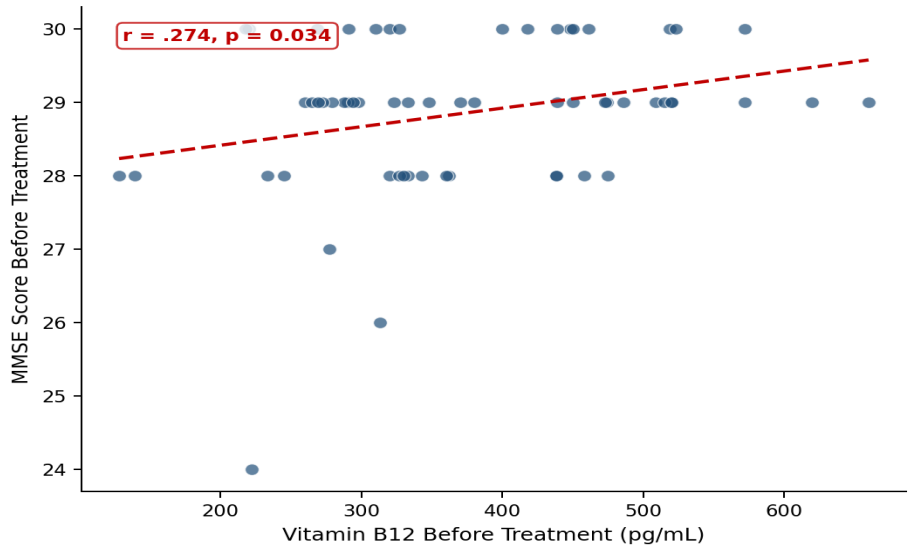

Figure 2. Scatter plot: Vitamin B12 before treatment vs MMSE before treatment (r=0.274, P=0.034).

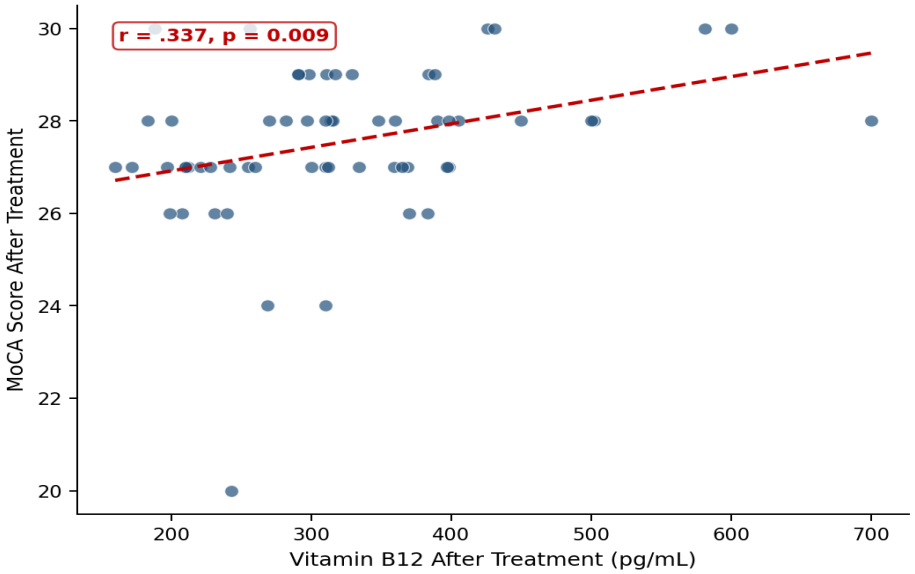

Figure 3. Scatter plot: Vitamin B12 after treatment vs MoCA after treatment (r=0.337, P=0.009).

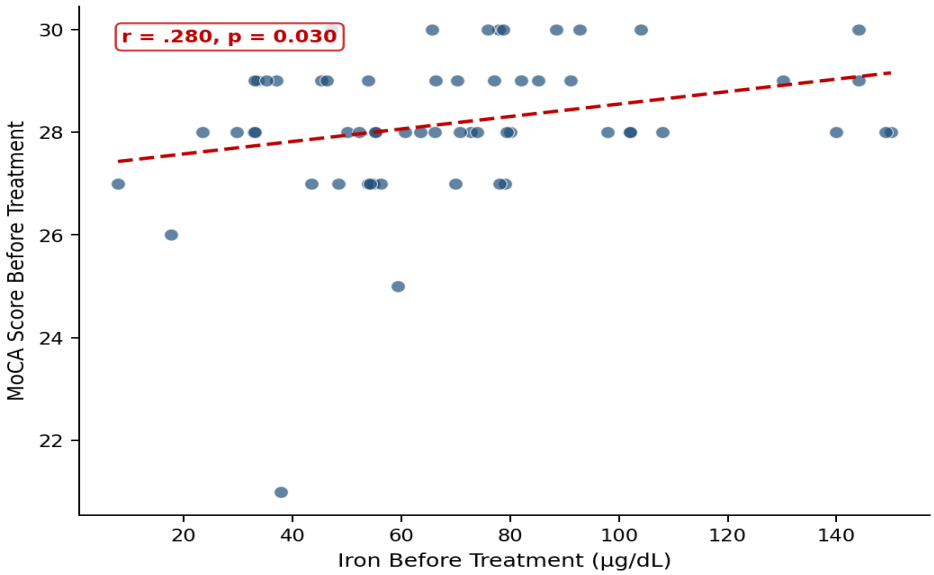

Figure 4. Scatter plot: Iron before treatment vs MoCA before treatment (r=0.280, P=0.030).

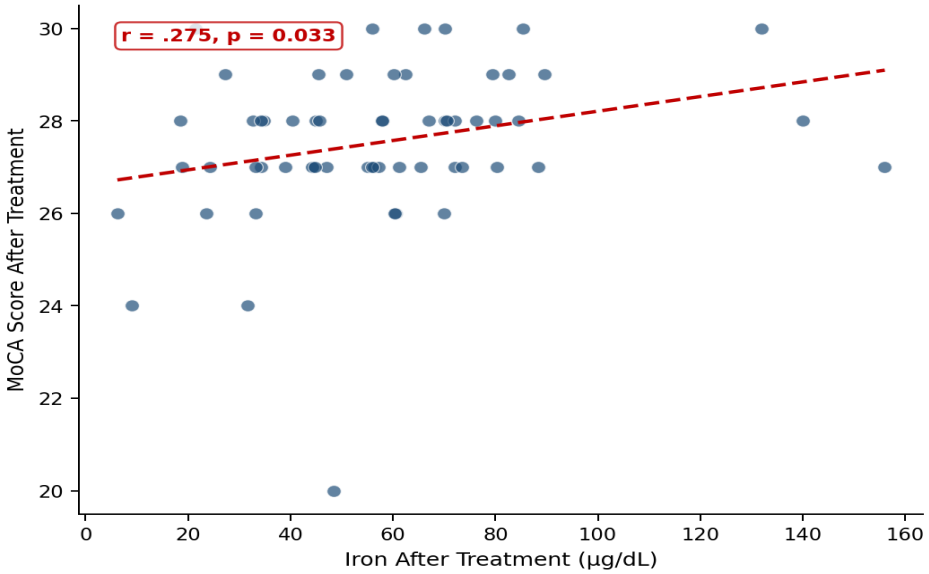

Figure 5. Scatter plot: Iron after treatment vs MoCA after treatment (r=0.275, P=0.033).

Effect of educational level

MMSE scores differed significantly across educational groups after treatment, with the uneducated subgroup (a) scoring lower than all other groups (b). MoCA scores were uniform across all groups (all a), consistent with MoCA's education adjustment. Post-treatment Vitamin B12 and Iron also differed across educational strata (Table 7).

Table 7. Vitamins, minerals and cognitive parameters by educational level after treatment (N=60)

Parameter	Uneducated (n=5)	Primary (n=13)	Secondary (n=7)	Institute (n=10)	University (n=25)
Vitamin B12 (pg/mL)	242.8±67.6 a	329.7±60.8 ab	242.1±76.5 a	305.9±92.1 ab	361.0±129.5 b
Magnesium (mmol/L)	1.89±0.33 a	1.91±0.45 a	2.00±0.28 a	1.98±0.28 a	1.98±0.34 a
Zinc (µg/dL)	39.1±13.9 a	53.9±29.7 a	41.7±14.6 a	48.0±28.3 a	59.1±25.2 a
Iron (µg/dL)	35.0±17.2 a	56.8±19.3 ab	53.0±23.2 ab	53.7±38.0 ab	65.1±30.2 b
Vitamin D3 (ng/mL)	16.9±5.4 a	30.6±21.7 b	28.5±15.3 ab	18.6±9.4 a	28.0±10.5 ab
MMSE (score)	27.0±1.9 a	28.9±1.0 b	28.9±1.1 b	28.7±1.0 b	29.0±0.8 b
MoCA (score)	26.4±1.5 a	27.9±1.2 a	27.9±1.2 a	27.5±1.6 a	27.5±2.0 a

Values are Mean±SD. Letters (a, b) below each value indicate post-hoc subgroups; same letter = no significant difference (α=0.05).

DISCUSSION

This study found that a two-month PPI course significantly reduced serum Vitamin B12, Magnesium, Zinc, and Iron, and produced a cognitive decline measurable by MoCA but not MMSE. Selective correlations of Vitamin B12 and Iron with MoCA scores indicate a nutritional contribution to the cognitive change detected.

Vitamin B12 showed a significant decrease (P=0.007), similar to other studies associating PPI use with B12 deficiency. The well-accepted mechanism explaining this effect is PPI-induced reduction of gastric acid levels, which are crucial for the release of protein-bound dietary B12 from food, reducing the amount of free B12 available for intrinsic factor binding and ileal absorption[20,21].Cognitive impairment is thought to occur through two B12-dependent pathways: the homocysteine pathway, in which increased homocysteine levels following B12 reduction may result in neuroinflammation, oxidative stress, and hippocampal atrophy. The other pathway is the S-adenosylmethionine (SAM)-dependent methylation pathway, in which reduced SAM availability impairs methylation of myelin basic protein and neurotransmitter precursors. Since this study examines short-term depletion and cognition linkage, SAM depletion may offer a more plausible explanation for short-term cognitive changes, as reductions in methyl donor availability can manifest earlier compared with structural myelin alterations[10].

Magnesium has also shown significant decrease (P=0.044), that has previously explained by other studies as the result of inhibition of TRPM6 and TRPM7 intestinal channels caused by PPI use that are important for Mg^{2+} uptake[22,5]. As a result of magnesium depletion, microglia will be activated causing the release of pro-inflammatory cytokine, which will cause calcium influx as a result of reversing the physiological NMDA receptor block eventually excitotoxic neuronal injury will result. Collectively neurodegeneration and cognitive decline will result from all the previous consequences[12]. Regardless of lower magnesium levels after two months of PPI treatment, no significant correlation was found linking this decrease with lower cognitive levels, implying that two months of PPI therapy did reduce magnesium level but not to an extent enough to cause detectable cognitive decline at least as assessed with the used tests.

Zinc fell significantly (P=0.005), consistent with pH-dependent reduction in its intestinal solubility and bioavailability — PPI use significantly impairs micronutrient absorption at the epithelial barrier level[23]. In the brain, Zinc regulates synaptic transmission, neuroplasticity, and antioxidant defence; its deficiency is associated with cognitive decline and elevated dementia risk[13]. No significant cognitive correlation was observed, likely reflecting the requirement for more prolonged or severe Zinc deficiency before central effects become measurable on standard screening tools.

Iron decreased significantly (P=0.033). Gastric acid is required to solubilise dietary non-heme iron from food complexes and to reduce ferric to ferrous iron via duodenal cytochrome B, the form transported by DMT-1; ascorbic acid, whose efficacy is also acid-

dependent, facilitates this reduction[25,26]. This explains why PPI-induced hypochlorhydria reduces iron bioavailability, consistent with published evidence on PPI-associated iron deficiency[24]. Iron correlated with MoCA at both timepoints (P=0.030; P=0.033) but not with MMSE, consistent with iron's role in dopaminergic and serotonergic neurotransmitter synthesis and mitochondrial neuronal energetics[11]. Subclinical iron depletion can impair iron-dependent neuronal enzyme activity before anemia develops[11].

Vitamin D3 increased non-significantly (P=0.485). Vitamin D3 exerts neuroprotective effects through brain receptors, facilitating amyloid clearance and neurotrophic signaling; higher brain 25-hydroxyvitamin D3 is associated with 25–33% lower odds of dementia and MCI[14]. Even with this important role of Vit D3 on cognition performance, Vit D3 was not correlated with either cognitive test. Conversely, Vit D3 showed non-significant increase that could be due to the timing of the study that took many months during summer months exposing the patients to higher solar UVB intensity of in Kurdistan or the improved patient's oral intake following relief from GERD symptoms counteracting PPI related vitamin D3 reduction.

When the two drugs' effects on micronutrients was evaluated independently they both showed significant decrease of Vitamin B12, Zinc, Iron, and MoCA score, while MMSE and Vitamin D3 remained unchanged with either of the two drugs. Magnesium showed significant decrease only with Dexlansoprazole group (P=0.043) but the decrease was insignificant with esomeprazole (P=0.133). However, magnesium reduction between-groups was non-significant (P=0.818), similar to previous findings regarding PPI hypomagnesaemia being a class effect rather than a drug-specific side effect[22].

MMSE showed no reduction after two months of PPI treatment (P=0.526) unlike MoCA the recorded significant reduction in the scores (P=0.004).MMSE test sensitivity is limited to moderate-to-severe cognitive impairment which is well documented regarding it's sensitivity[27]. While MoCA was developed targeting MCI and since it tests executive function, attention, and delayed recall — domains that are affected by nutritional depletion even if not big enough to be detected by MMSE [19]. The pattern of change in cognitive tests (63.3% MoCA decline vs 18.3% MMSE decline) backs up that MoCA was able to detect cognitive decline that overpassed MMSE detection.

This is, to the best of our knowledge, the first prospective study to apply both MoCA and MMSE as paired longitudinal measures to quantify the cognitive impact of PPI therapy. Prior studies have relied on administrative databases, neuroimaging, or specialist computerised platforms[28], not on validated bedside tools calibrated for early cognitive change.

Only Vitamin B12 and Iron correlated with cognitive scores, exclusively with MoCA. The pre-treatment B12-MMSE correlation (r=0.274, P=0.034) suggests patients with lower baseline B12 already had subtly reduced cognitive scores, reflecting B12's neuronal methylation function[10,21]. After treatment, B12 correlated with MoCA (r=0.337, P=0.009), consistent with MoCA's sensitivity to B12 decline and the faster-acting SAM methylation pathway[10]. Age correlated with MMSE before (r=−0.295, P=0.022) and after treatment (r=−0.308, P=0.017) but not with MoCA. The uneducated subgroup had the highest mean age (55.0±13.2 years), and the inverse age-education relationship was significant (r=−0.440, P<0.001). MMSE scores was different across educational groups unlike MoCA scores that showed more uniformity, consistent with MoCA's education adjustment and reduce the likelihood that education factor was MoCA decline.

CONCLUSION

1.PPI two months of treatment was enough to cause significant reduction in serum Vitamin B12, Magnesium, Zinc, and Iron.

2. Vitamin D3 didn't decline, on the opposite it showed non significant increase that could be due to sun exposure during the treatment period or better food intake after GERD symptoms were controlled by PPI treatment.

3. Cognitive decline was detected by MoCA (significant decline) while MMSE showed no detection confirming the higher sensitivity of MoCA to mild cognitive decline.

4. Esmoprazole and Dexlansoprazole showed similar effects on both micronutrients' levels and cognitive tests behaviors.

5. Cognitive decline assessed by MoCA was shown to be correlated with only Vitamin B12 and Iron.

6. Magnesium, Zinc, and Vitamin D3, even with their decline, they were not correlated with cognitive performance regardless of their neuroprotective roles, implying that to have effect on cognitive function greater periods of depletion or more severe decrease to become measurable.

7. The age-MMSE correlation was largely attributable to educational confounding; MoCA's scoring with education consideration and adjustments was clear through the uniform results across all educational groups.

8. This study provides the first prospective paired application of both MoCA and MMSE as pre- and post-treatment cognitive outcome measures in a PPI therapy trial.

ACKNOWLEDGEMENTS

We wish to express our sincere gratitude to the staff of PAR Private Hospital, Erbil, for their assistance in patient recruitment and sample collection.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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