



## Real -World Multicentre Study on Micronutrient Adjunct Therapy in Chronic Fatigue Syndrome with Type 2 Diabetes

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### ABSTRACT

**Background:** Chronic Fatigue Syndrome (CFS) is a debilitating condition often coexisting with Type 2 Diabetes Mellitus (T2DM), compounding the burden of fatigue, metabolic dysfunction, and poor quality of life. Emerging evidence suggests that micronutrient deficiencies may play a significant role in the pathophysiology of both conditions. This study explores healthcare professionals' (HCPs) real-world experience regarding the effectiveness of micronutrient adjunct therapy in managing patients with coexisting CFS and T2DM in India. **Methods:** This multicentre, questionnaire-based observational study was conducted among 52 HCPs, including endocrinologists, diabetologists, and general physicians across India. Data were collected regarding the last 10 patients with CFS and T2DM managed using multi-nutrient formulations. The 15-item survey focused on glycemic control, fatigue, sarcopenia, dietary compliance, neuropathic pain, and quality of life. Descriptive statistical analysis was performed. **Results:** The majority of HCPs (50.0%) reported that fewer than 6 out of 10 patients had uncontrolled diabetes with CFS. Fatigue (44.2%) and inability to perform daily tasks (34.6%) were the most commonly reported symptoms. Micronutrient therapy resulted in 50–60% fatigue reduction (51.9% of HCPs), with improved visual analogue scale scores reported by the majority. Improvements in glycemic control (76.9%), relief from neuropathic pain (94.2%), and enhanced muscle strength and work performance, particularly in sarcopenic patients, were also observed. Patients with multiple comorbidities, including sarcopenia, hypertension, and chronic kidney disease, showed the greatest benefit from combined therapy with B12, essential amino acids, and minerals. **Conclusion:** Micronutrient adjunct therapy appears effective and well-tolerated for managing CFS with T2DM, improving fatigue, glycemic control, muscle strength, and quality of life, particularly in patients with sarcopenia. Further trials are needed to confirm and optimise these outcomes.

**Keywords:** Chronic Fatigue Syndrome, Type 2 Diabetes Mellitus, Micronutrient, Fatigue, Sarcopenia

### INTRODUCTION

Diabetes mellitus is one of the most common chronic metabolic diseases worldwide, posing a significant threat to global health. According to the International Diabetes Federation, approximately 463 million adults aged 20–79 were living with diabetes in 2019, with projections indicating this number could rise to 578.4 million by 2030 [1]. Among the numerous complications of type 2 diabetes mellitus (T2DM) are changes in micronutrient status, as indicated by human and animal research. T2DM patients have lower plasma levels and higher urinary excretion of certain micronutrients than healthy persons, which can detrimentally influence glucose regulation and insulin sensitivity, and lead to disease development and complications [2].

Aside from metabolic disturbances, T2DM is also frequently complicated by sleep disorders and chronic fatigue, which impair disease control and considerably reduce quality of life [3]. Fatigue, including both physical and mental aspects, is a frequent and disabling symptom, presenting as a subjective experience of decreased ability for physical and mental effort [1].

In the same way, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic multisystem disease characterised by persistent, unexplained fatigue and other symptoms that drastically limit daily function. With a worldwide prevalence of between 0.1% and 0.8%, ME/CFS generates a significant individual and socioeconomic burden [4]. Even though its pathophysiology remains to be fully understood, new evidence points towards an association between micronutrient deficiencies and the initiation or severity of CFS symptoms [5].



Recent research has emphasised the value of micronutrient supplementation in fatigue and metabolic derangement management. Sufficient intake of micronutrients like vitamins D, B-complex, E, and C, magnesium, zinc, and chromium has been linked with better metabolic profiles and insulin sensitivity in both metabolic syndrome and T2DM patients [2,6,7]. Furthermore, greater dietary adequacy of micronutrients has been linked to improved sleep quality and quantity in T2DM patients, albeit its direct effect on chronic fatigue is less well characterised [3].

Micronutrient deficiencies, chronic fatigue, and metabolic dysfunction commonly overlap in CFS and T2DM, prompting interest in adjunctive micronutrient therapy to improve fatigue and overall health. While early evidence supports targeted supplementation, particularly in those with deficiencies, well-designed clinical trials are needed to define optimal regimens and assess their effects on fatigue and metabolic outcomes. The present study provides insights from healthcare professionals (HCPs) on the use of micronutrient adjuvant therapy for patients with chronic fatigue syndrome with T2DM.

## Methods:

### *Study design*

This questionnaire-based, multi centred study was designed to evaluate the real-world use of micronutrient adjunct therapy in the management of chronic fatigue syndrome with type 2 diabetes as reported by HCPs across India. All study related findings and data presented in this report were based on expert opinions.

### *Study questionnaire*

The study questionnaire was designed based on clinical guidelines, existing literature and experts' opinions. It included 15 questions focusing on chronic fatigue syndrome with T2DM, including areas such as glycemic control, neuropathic pain, dietary compliance, sarcopenia, and patient response to multi-nutrient adjunct therapy. The questionnaire focused on the last 10 patients with CFS and type 2 diabetes treated with a multi-nutrient formulation. The study protocol was approved by the independent ethics committee. (ACEAS- Independent ethics committee, Ahmedabad, India, Date of approval: 16 Oct 2024).

### *Data collection method*

The HCPs mainly including endocrinologists, diabetologists and general physicians, participating in the study were provided with a concise overview of the study's nature and the process for completing the questionnaire. The questionnaire was given to HCPs either in person, or through online platforms, as per the HCP's convenience.

### *Data analysis*

Responses to questions were entered into Microsoft excel. Descriptive analysis was performed and the outcome was presented as percentages.

## Results:

A total of 52 HCPs were included in this study. The majority of HCPs (50.0%) reported that less than 6 out of 10 patients had uncontrolled diabetes with chronic fatigue syndrome (CFS). While 38.5% of HCPs reported that 7 out of 10 patients have uncontrolled diabetes with CFS (Figure 1). A significant portion (40.4%) of HCPs observed that less than 6 out of 10 patients had diabetic neuropathic pain with CFS (Figure 1).

Physicians shared their clinical experience with 10 patients regarding risk factors for CFS. A total of 46.2% HCPs reported that uncontrolled diabetes and poor exercise regimen (19.2%) were major risk factors for CFS (Table 1). According to 42.3% of HCPs, less than 6 out of 10 patients diagnosed with sarcopenia were non-compliant with diet and had no balanced diet (Figure 1).

Fatigue, as the chief complaint of CFS, was reported by 44.2% HCPs, while 34.6% HCPs reported inability to do routine work. Around 11.5% and 7.7% of HCPs noted impaired sleep and inability to concentrate at work as chief complaints of CFS, respectively (Table 1).

The visual analogue scale (VAS) was analyzed for the patients treated with multi-nutrient formulations. The majority (50.0%) of HCPs found average VAS scores in the range of 3 - 4 in CFS patients treated with multi-nutrient formulations, whereas 30.8% of them found average VAS scores in the range of 5 - 6. Reduction in fatigue was evaluated on VAS; 51.9% of HCPs observed a 50-60% reduction, and 25.0% reported a 60-70% reduction. Only 7.7% observed more than a 70% reduction in fatigue (Table 2).



According to 26.9% of HCPs, 7 out of 10 patients showed improved work, sleep and quality of life after treatment with multi-nutrients and 23.1% noted, 8 out of 10 patients showed improvement (Table 2). Even improvement in glycemic control was reported who were treated with multi-nutrients by the majority (76.9%) of HCPs (Figure 2a). Also, 94.2% of HCPs reported relief of painful neuropathic symptoms with the use of multi-nutrients (Figure 2b).

A combination of chief complaints, such as reduced muscle strength, inability to perform routine work, and impaired social activity, was reported by the largest proportion (65.4%) of HCPs, and only a few (9.6%) reported inability to perform routine work (Table 1).

Patients with sarcopenia were treated with essential amino acid (EAA) along with B12, vitamins and minerals and showed improved muscle strength, better capacity to perform routine work and to support metabolic functions, according to 69.2% of HCPs (Figure 3). Additionally, the combination therapy of B12 and peripheral artery disease (PEA) also showed improved muscle strength, better capacity to perform routine work and to support metabolic functions as reported by 80.8% of HCPs (Figure 3).

The majority (76.9%) of HCPs noted that reduced muscle mass, frailty and reduced quality of life with higher mortality were observed in CFS patients along with co-morbidities like hypertension, diabetes, peripheral artery disease and congestive heart failure (Table 3). Patients with sarcopenia, diabetes mellitus, hypertension and chronic kidney disease have the maximum benefit from B12 along with EAA and micronutrients (Table 3).

## Discussion

The present study provides valuable insights into the real-world use of micronutrient adjunct therapy in the management of CFS with T2DM among HCPs. Of all 52 HCPs, 50.0% reported that fewer than 6 out of 10 patients had uncontrolled diabetes with chronic fatigue syndrome CFS, while 38.5% indicated that 7 out of 10 patients had both uncontrolled diabetes and CFS. A cross-sectional descriptive study by Hanjong et al. highlighted that diabetes distress, depressive symptoms, and related symptoms mediate the link between glucose control and fatigue in T2DM. Their findings indicated that in patients with an HbA1c  $\leq 7\%$ , fatigue was more strongly associated with diabetes distress and symptoms, whereas in those with poorer glycaemic control (HbA1c  $> 7\%$ ), fatigue was indirectly related to glucose control itself. Similarly, a cross-sectional observational study by Martine et al. involving 214 patients with type 1 diabetes mellitus found that 40% experienced chronic fatigue [8].

A significant portion (40.4%) of HCPs in the present study observed that less than 6 out of 10 patients experienced diabetic neuropathic pain alongside CFS. This observation is consistent with findings from a large observational study conducted by Abbott et al. involving 15,692 diabetic patients, which reported the prevalence of painful diabetic neuropathy (PDN) at 21% of patients using validated symptom and disability scores. While PDN is relatively common, these findings affirm that it does not affect the majority of diabetic patients with CFS [9]. In evaluating clinical risk factors for CFS, 46.2% of HCPs identified uncontrolled diabetes, and 19.2% highlighted a poor exercise regimen. A study by Natalia et al. found that sedentary behaviour, such as prolonged sitting, may elevate CFS risk, though physical activity itself was not directly associated with fatigue onset [10]. Regarding nutritional compliance, 42.3% of HCPs reported that fewer than 6 out of 10 patients with sarcopenia had a balanced diet. These results are in line with findings from the Taiwan Nutrition and Health Survey by Jin et al., which revealed that sarcopenic adults had significantly lower Healthy Eating Index scores, particularly in vegetable and dairy intake. Adherence to national dietary guidelines was inversely associated with the risk of sarcopenia, especially in older adults [11].

1. Fatigue was the most common presenting symptom of CFS, reported by 44.2% of HCPs, followed by an inability to perform routine activities (34.6%). These observations are relevant to the study by Murihead et al. by using the EQ-5D questionnaire, in which 97.3% of participants reported limitations in usual activities, underscoring the central role of fatigue in daily functional impairment [12]. Assessment of treatment response using the VAS revealed that 50.0% of HCPs observed average fatigue scores in the 3–4 range following multi-nutrient therapy, while 51.9% reported a 50–60% reduction in fatigue. These observations are supported by a phase 2 clinical trial by Montoya et al., where patients receiving KPAX002—a micronutrient and low-dose stimulant formulation reported improved fatigue scores, particularly in those with higher symptom severity [13].

2. A study by Lacasa et al. assessed the use of yeast beta-glucan as a nutritional supplement and/or functional food to prevent or reduce cognitive dysfunction in patients with ME/CFS through a 36-week randomised trial. Significant improvements in cognitive fatigue, sleep quality, and overall quality of life were reported among ME/CFS patients treated with a micronutrient blend including beta-glucan, vitamin D3, B6, and zinc [14]. These findings align well with the present study, with 26.9% of HCPs reporting improvements in work performance, sleep quality, and overall quality of life in 7 out of 10 patients receiving multi-nutrient. Additionally, 76.9% of HCPs observed improved glycemic control, and 94.2% noted relief from neuropathic pain following treatment. The most common CFS symptom combination, reduced muscle strength, difficulty with daily tasks, and impaired social functioning, was reported in 65.4% of cases. After treatment with essential amino acids, vitamin B12, and minerals, 69.2% of HCPs



noted improved muscle strength and function in sarcopenic patients. Similar benefits were observed by 80.8% of HCPs when B12 was combined with palmitoylethanolamide, underscoring its role in muscle metabolism.

3. Additionally, 76.9% of HCPs reported that patients with CFS and comorbidities such as hypertension, diabetes, peripheral artery disease, and heart failure often experienced muscle mass loss, frailty, and reduced quality of life conditions linked to increased mortality risk and noted that patients with sarcopenia, diabetes, hypertension, and chronic kidney disease benefited most from B12, EAA, and micronutrient therapy. These clinical observations are supported by a recent analysis of NHIS data (2021–2022) by Denu et al., which found that CFS was significantly associated with higher odds of cardiovascular disease, even after adjusting for major cardiometabolic risk factors [15]. Similarly, another study by Liu et al. by a cross-sectional NHANES study, reported that nutrient patterns rich in vitamin B12, calcium, and vitamins A and D were associated with greater muscle mass and lower risk of sarcopenia, even in the presence of chronic comorbidities [16].

The study has a few limitations. A small sample size may limit the generalizability of findings, as the responses may not adequately represent the larger population of HCPs. The use of a self-reported questionnaire introduces the potential for response bias. The questionnaire may not cover all relevant aspects of the subject matter.

### Conclusion

The findings from the current study suggest that micronutrient adjunct therapy is generally well tolerated and perceived as beneficial in the management of CFS with T2DM. Most HCPs indicated that there was an improvement in the reduction of fatigue, control of glycemia, alleviation of neuropathic pain, muscle strength, and overall quality of life. These improvements were particularly significant for those with associated sarcopenia and cardiometabolic comorbidities. Nonetheless, heterogeneity in treatment response, clinical practice, and patient compliance emphasises the requirement for additional randomised controlled trials to establish optimal combinations of nutrients, dosing regimens, and long-term clinical outcomes in various populations of patients.

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### REFERENCES:

1. Bi Y, Zhang L, Li X, Kan Y, Li S, Zou Y, Liu L, Yuan Y, Gong W, Zhang Y. Contributing factors of fatigue in patients with type 2 diabetes: A systematic review. *Psychoneuroendocrinology*. 2021;130:105280.
2. Kaur B, Henry J. Micronutrient status in type 2 diabetes: a review. *Adv Food Nutr Res*. 2014;71:55-100.
3. Kazeminejad S, Esfahani EN, Azadbakht L. Association between dietary micronutrient adequacy index and sleep quality, sleep duration and chronic fatigue in patients with type 2 diabetes. *J Diabetes Metab Disord*. 2025;24(1):135.
4. Arron HE, Marsh BD, Kell DB, Khan MA, Jaeger BR, Pretorius E. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: the biology of a neglected disease. *Front Immunol*. 2024 ;15:1386607.
5. Akduman G, Kurtbeyoglu E, Gunes FE. Can we reduce the symptoms of chronic fatigue syndrome by regulating micronutrients? A review. *Current Nutrition & Food Science*. 2023;19(5):509-18.
6. Sunday Kolawole. Micronutrients in Metabolic Syndrome: A Comprehensive Review. *Food Sci Nutr Res*. 2025; 8(2): 1-6.
7. Younes, S. The role of micronutrients on the treatment of diabetes. *Human Nutrition & Metabolism*. 2024; 35, 200238.
8. Goedendorp MM, Tack CJ, Stegink E, Bloot L, Bazelmans E, Knoop H. Chronic fatigue in type 1 diabetes: highly prevalent but not explained by hyperglycemia or glucose variability. *Diabetes Care*. 2014;37(1):73-80.
9. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care*. 2011 Oct;34(10):2220-4.
10. Palacios N, Molsberry S, Fitzgerald KC, Komaroff AL. Different risk factors distinguish myalgic encephalomyelitis/chronic fatigue syndrome from severe fatigue. *Sci Rep*. 2023;13(1):2469.
11. Liou YJ, Giovannucci E, Chien WC, Wu LW. Evaluation of Dietary Guideline Adherence and Risk of Sarcopenia in Elder Taiwanese. *Food Sci Nutr*. 2025 ;13(6):e70343.
12. Muirhead NL, Vyas J, Ephgrave R, Singh R, Finlay AY. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Impact on Quality of Life (QoL) of Persons with ME/CFS. *Medicina (Kaunas)*. 2024 ;60(8):1215.
13. Montoya JG, Anderson JN, Adolphs DL, Bateman L, Klimas N, Levine SM, Garvert DW, Kaiser JD. KPAX002 as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a prospective, randomized trial. *Int J Clin Exp Med*. 2018;11(3):2890-900.



14. Lacasa M, Alegre-Martin J, Sentañes RS, Varela-Sende L, Jurek J, Castro-Marrero J. Yeast Beta-Glucan Supplementation with Multivitamins Attenuates Cognitive Impairments in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients*. 2023;15(21):4504.
15. Denu MKI, Revoori R, Eghan C, Kwapong FL, Hillman A, Normeshe CA, Berko KP, Aidoo EL, Buadu MAE. Association between chronic fatigue syndrome/myalgic encephalomyelitis and cardiovascular disease. *Sci Rep*. 2025 ;15(1):2294.
16. Liu Y, Liu X, Duan L, Zhao Y, He Y, Li W, Cui J. Associations of micronutrient dietary patterns with sarcopenia among US adults: a population-based study. *Front Nutr*. 2024;11:1301831.

**Table 1:** Risk factors and chief complaints of CFS and sarcopenia

Parameters	Response of HCPs (N=52)
<b>Risk factors for CFS</b>	
Uncontrolled diabetes	24 (46.2)
Hyperhomocysteinemia	2 (3.8)
Obesity	3 (5.8)
Poor exercise regimen	10 (19.2)
Work stress	2 (3.8)
Anxiety	4 (7.7)
Depression	6 (11.5)
Poor Sleep	1 (1.9)
<b>Chief complaints of CFS</b>	
Fatigue	23 (44.2)
Inability to do routine work	18 (34.6)
Inability to concentrate at work	4 (7.7)
Impaired social activity	1 (1.9)
Impaired sleep	6 (11.5)
<b>Chief complaints of sarcopenia</b>	
Reduced muscle strength	13 (25.0)
Inability to do routine work	5 (9.6)
Impaired social activity	-
All of the above	34 (65.4)
Data represented as n (%).	
CFS, chronic fatigues syndrome; HCPs, health care providers.	

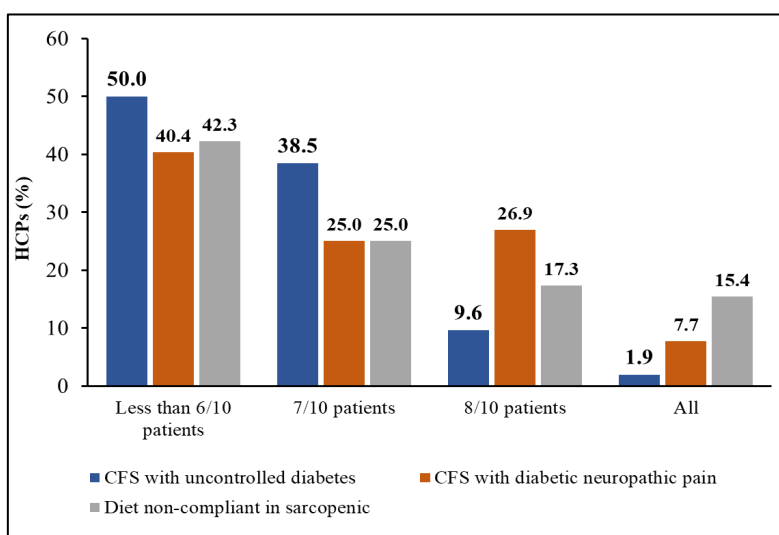
**Table 2:** The VAS score, improved quality of life with multi-nutrients and reduction in fatigue

Parameter	Response of HCPs (N=52)
<b>Average VAS score of CFS treated with multi-nutrient formulation</b>	
1-2	3 (5.8)
3-4	26 (50.0)
5-6	16 (30.8)
Greater than 6	7 (13.5)
<b>Percent reduction in fatigue on a VAS scale of 0 to 10</b>	
Less than 50%	8 (15.4)
50-60%	27 (51.9)
60-70%	13 (25.0)
Greater than 70%	4 (7.7)
<b>Improved work, sleep and quality of life treated with multi-nutrient formulation</b>	
All patients	11 (21.2)
9/10 patients	10 (19.2)
8/10 patients	12 (23.1)
7/10 patients	14 (26.9)
Less than 7/10 patients	5 (9.6)
Data represented as n (%).	
CFS, chronic fatigues syndrome; HCPs, health care providers; VAS, visual analogue scale.	

**Table 3:** Impact of chronic illness and benefits from B12, EAA with micronutrients

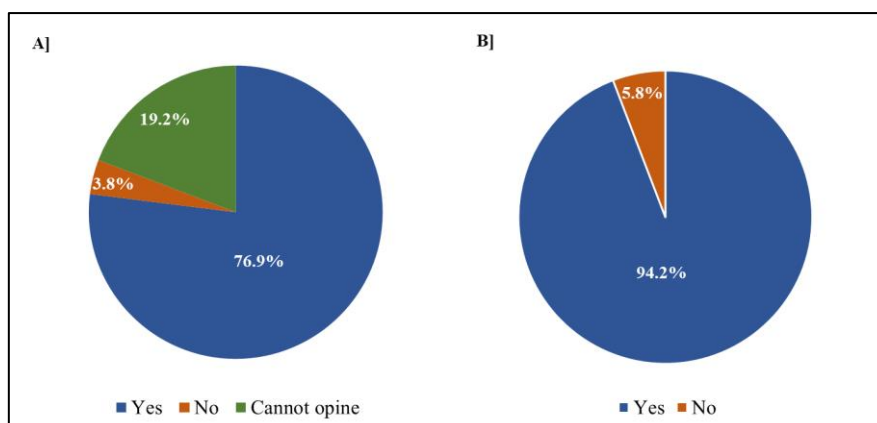
Parameters	Response of HCPs (N=52)
<b>Impact of chronic illnesses like hypertension, Diabetes, PAD, CHF</b>	
Reduced muscle mass	4 (7.7)
Frailty and reduced QOL	4 (7.7)
Higher mortality	4 (7.7)
All of the above	40 (76.9)
<b>Patient experiencing the most benefit from B12 plus EAA and minerals therapy</b>	
Sarcopenic individuals	5 (9.6)
Diabetes mellitus/hypertension	14 (26.9)
Chronic kidney disease	1 (1.9)
All of the above	32 (61.5)

Data represented as n (%).  
 CHF, congestive heart failure; EAA, essential amino acids; HCPs, health care providers; PAD, peripheral artery disease; QOL, quality of life.

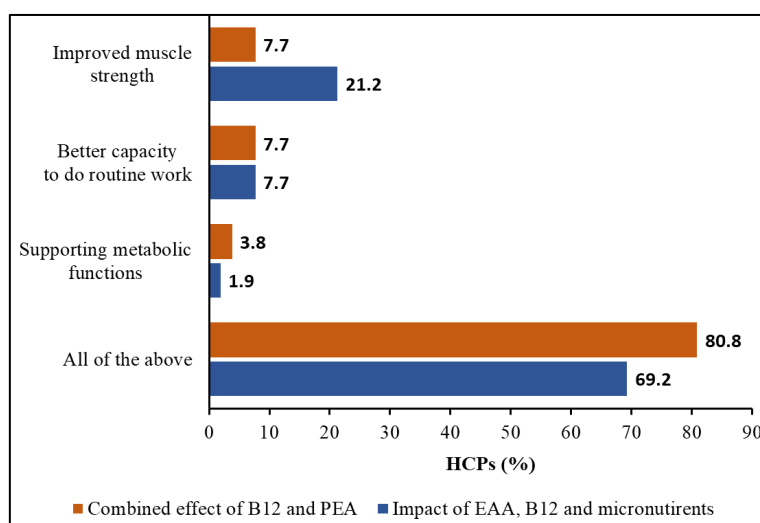


**Figure 1:** Responses of HCPs for comorbidities

CFS, chronic fatigue syndrome; HCPs, healthcare practitioners.



**Figure 2:** A] Glycaemic control and B] neuropathic symptoms with multi-nutrients



**Figure 3:** Impact of EAA, B12, micronutrients on sarcopenia and effect of B12 and PEA

EAA, essential amino acid; PEA, palmitoylethanolamide.

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Conflict of Interest Statement: All authors have nothing else to disclose.

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