The Journal of Nutrition, Health and Aging 28 (2024) 100256

Contents lists available at ScienceDirect

The Journal of Nutrition, Health and Aging

journal homepage: www.elsevier.com/locate/jnha

Original Article

The role of nutritional supplement on post-stroke fatigue: a pilot randomized controlled trial

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ARTICLE INFO

Keywords:
Fatigue
Stroke
Elderly
Nutritional supplement
Rehabilitation

ABSTRACT

Objectives: Post-stroke fatigue (PSF) is an experience characterized by an early feeling of exhaustion with fatigue, a lack of energy, and difficulty in exertion, both motor and cognitive. To counteract fatigue and limit its effects on activities of daily living, the use of vitamins and minerals is known in addition to the pharmacological approach. However, few studies have evaluated the effect of vitamin and mineral supplementation on fatigue management. SiderAL® Med is a food for special medical purposes with a complete formulation containing vitamins, sucrosomal minerals, copper and algal calcium. The aim of the study is to evaluate whether nutritional supplementation with SiderAL® Med improves the symptom of fatigue and motor and cognitive function in stroke patients.
Design: This is a pilot, randomized study with a control group.
Setting: Post-Acute Rehabilitation Unit of the Fondazione Policlinico "A. Gemelli" IRCCS.
Participants: Twenty-four patients with stroke outcomes, admitted to rehabilitation, were recruited and randomized into the experimental group (Sid-G) and the control group (CG).
Intervention: The Sid-G patients, in association with the pharmacological and rehabilitation therapy foreseen during hospitalization, took SiderAL® Med, one sachet per day for 8 weeks, while the CG patients underwent only the pharmacological and rehabilitation therapy foreseen in the daily routine.
Measurements: All patients were assessed at baseline (T0), after 4 weeks (T1), after 8 weeks (T2) and after 12 weeks (T3) for motor and cognitive fatigue, balance, walking, functional capacity, cognitive performance, autonomy, quality of life and body composition.
Results: Both Sid-G and CG patients showed significant improvement on most rating scales between T0-T1-T2-T3 ($p = 0.0001$). When comparing the two groups, a statistically significant difference emerged in favor of Sid-G with regard to motor fatigue ($p = 0.007$), cognitive fatigue ($p = 0.009$) and total fatigue ($p = 0.034$); balance ($p < 0.001$), functional capacity ($p < 0.001$); cognitive performance ($p = 0.004$); bone mineral content ($p = 0.005$), lean mass ($p = 0.005$), total mass ($p < 0.001$) and percentage of fat mass ($p = 0.039$).
Conclusion: Nutritional supplementation with SiderAL® Med, in concert with intensive rehabilitation treatment, appears to be effective in managing fatigue and improving motor and cognitive performance and body composition, representing a valuable tool to associate with rehabilitation treatment in stroke patients.

1. Introduction

Fatigue, which is commonly defined as a sensation of tiredness during or after usual activities, or a feeling of insufficient energy to initiate these activities [1,2], is one of the most common secondary conditions among patients with stroke [3].

The definition Post Stroke Fatigue (PSF) is controversial because of its subjective perception. It can be described as a multidimensional motor-

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http://doi.org/10.1016/j.jnha.2024.100256
Received 29 March 2024; Received in revised form 24 April 2024; Accepted 24 April 2024
Available online xxx

perceptual, emotional and cognitive experience characterized by a feeling of early exhaustion with tiredness, lack of energy and difficulty making efforts. It can develop during physical or mental activity and usually does not improve with rest [4–7]. The prevalence of PSF in patients is high, affecting one out of two patients. PSF can have a negative impact on recovery, affecting participation to rehabilitation training [8]. PSF in the first period after stroke is high and has a significant negative impact on stroke survivors' activities of daily living [9,10]. In fact, PSF is characterized by overwhelming tiredness, lack of energy to carry out daily activities, the need for long periods of rest, greater fatigue in daily activities compared to the period before the acute event and feeling unpredictable tiredness for no apparent reason. Recently, the Stroke Recovery and Rehabilitation Roundtable presented a consensus and a roadmap for research in post-stroke fatigue underling its importance and prevalence in stroke survivors [11]. There are no evidences about the effectiveness of pharmacological treatment on PSF [12]; moreover, non-pharmacological interventions did not give better findings [13]. To counteract this type of fatigue and its effects on daily life activities, benefits are reported from Modafinil, psychoeducational interventions and neuromodulation therapies [14–16]. A multidisciplinary approach including drugs, physical exercise and psychological treatment resulted more effective [7,17–19].

An increasing amount of research suggests that neuroprotective diets and nutritional supplements may be associated with better brain repair and outcomes for post-stroke rehabilitation [20]. Malnutrition after a stroke is associated with lower functional recovery and worse death rates. Patients should think about nutritional supplementation because there is a correlation between long-term outcomes after a stroke and nutritional status [21]. A few pieces of data elucidated the mechanics behind the connection between stroke and nutrition. For the rehabilitation of ischemic stroke patients, nutritional supplementation may be beneficial in certain situations and prevent further complications [22,23].

The use of vitamins and minerals may help in mitigating, among others, the effects of fatigue [24]. Nutrients provide the energy necessary to maintain the structural and biochemical integrity of the organism. Energy is associated with a feeling of well-being, increased resistance and vitality that often affect the ability to undertake daily physical or cognitive activities and social relationships, opposite to fatigue [25].

A common feature of fatigue is the "sense of energy depletion", which can objectively be related to an insufficient amount of energy. Physical and cognitive tiredness occurs when the continuous demand for energy from the brain and muscles is not satisfied. In humans, food macro-nutrients provide the fuel necessary, among other things, to carry out physical activity [26]. In fact, mineral salts and vitamins are fundamental for the production of cellular energy, for preventing muscle loss, for the maintenance of brain structures and for allowing the formation of intercellular connections [27,28].

When the intake of vitamins and mineral salts is adequate, their biochemical properties translate into normal physiological functions; a lower intake of mineral salts and vitamins is associated with lethargy and physical and cognitive fatigue. However, few studies have evaluated the effect of vitamin and mineral supplementation for the management of physical and cognitive fatigue [29–32]. Furthermore, although there is a clear relationship between malnutrition and stroke, there is no evidence regarding the role of nutritional supplementation in post-stroke fatigue.

Food for Special Medical Purposes are products formulated for the dietary management of patients with proven nutritional needs, for whom modifications to the normal diet are not sufficient [33]. In some situation, patients may have nutritional needs related to a limited, disturbed or altered ability to take, digest, absorb, metabolize or eliminate certain nutrients; in other cases, however, nutritional needs may be determined by specific clinical conditions [34,35]. Sucrosomial® technology applied to minerals, and in particular to iron represents a valid option for individuals with intolerance to iron salts or those for whom iron salts are inefficacious with a lower cost and fewer side effects [36–38]. SiderAL® Med (Pharmanutra SpA; Pisa, IT) is a food for Special Medical Purposes, with a complete formulation that contains vitamins, Sucrosomial® minerals (Iron, Iodine, Magnesium, Zinc and Selenium), copper and algal calcium, with enhanced dosages to meet particular nutritional needs.

As highlighted so far, there are currently few studies evaluating the effect of nutritional supplementation on fatigue, but none of them considers post-stroke fatigue. This study therefore aims to try to fill this gap. Thus, considering the evidences from the literature, the aim of the present study is to evaluate whether the nutritional supplement with SiderAL® Med improves the fatigue symptom, motor and cognitive function in patients with stroke outcomes. In particular, the primary aim of the present study is to evaluate the effects of the nutritional supplement with SiderAL® Med on physical and cognitive fatigue. Moreover, secondary objectives of the study are to evaluate the effects of the nutritional supplement with SiderAl® Med on motor (balance and walking) and cognitive performance (sustained attention), quality of life and bone mineralization status.

2. Methods

2.1. Study design and populations

This is a pilot, randomized controlled study.

Patients with stroke outcomes who met inclusion criteria, admitted to Post-Acute Rehabilitation Unit of the Fondazione Policlinico “A. Gemelli” IRCCS, were included in the study.

Patients were divided into two groups by randomization. One group (experimental group, Sid-G), in association with the pharmacological therapy, will take the nutritional supplement with SiderAL® Med (1 sachet per day for 28 consecutive days), while another group will continue the clinical, pharmacological and rehabilitation treatment as per the daily routine (control group, CG).

Inclusion criteria were the following: age $\geq$55 years; ischemic or hemorrhagic stroke outcomes documented through neuroimaging techniques (magnetic resonance imaging or computed tomography); latency from the acute event between 1 and 6 months; cognitive abilities that allow you to carry out simple orders and understand the physiotherapist's instructions [assessed through the Token Test (score $\geq$ 26.5)]; ability to walk independently or with little assistance; ability to understand and sign the informed consent.

On the other side, these are the exclusion criteria: age <55 years; intake > 3000 IU/day of Vitamin D; therapy with Vitamin K antagonists; conditions that cause excess blood electrolytes; diagnosis of metabolic diseases due to mineral accumulation (e.g. hemochromatosis, Wilson); patients on dialysis; systemic, cardiac, or neurological pathologies, including conditions other than stroke that make walking risky or cause motor deficits; oncological pathologies; orthopedic or postural problems; presence of plantar ulcers; partial or total amputation of segments of the foot and inability to provide informed consent.

This study was conducted in accordance with the specific national laws and ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments. The Territorial Ethics Committee (Prot. No. 0031523/22, September 29, 2022) approved the study protocol, and informed consent was obtained from each participant prior to any study procedure (ClinicalTrials.gov ID: NCT05728229).

2.2. Measurements

At the beginning of the study (T0), the following information were collected: demographic and anthropometric data (age, sex, education, body mass index); clinical characteristics (comorbidities, date of the event, etiology of the event, latency from the event, date of surgery, current pharmacological therapies).

Clinical and instrumental assessments were done at baseline (T0), at the end of 4 weeks of hospitalization (T1), after 8 weeks (T2) and after 16

weeks (Follow-up, T3). The outcome assessors, rehabilitation therapists, and statistical analyst were blinded to the randomization of patients.

2.3. Clinical evaluation

In detail, the clinical evaluation included: (i) Fatigue, by using Modified Fatigue Impact Scale (MFIS) [39,40]; (ii) motor performance and balance, by Motricity Index (MI) [41,42], Berg Balance Scale (BBS) [43], Time Up&Go (TUG) [44]; Short Physical Performance Battery (SPPB) [45]; (iii) walking, by using Ambulation Index (AI) [46], Walking Handicap Scale (WHS) [47], Functional Ambulation Category (FAC) [48], 10-Meter Walking Test (10MWT) and 6-Minute Walking Test (6MWT) [49]; (iv) autonomy in ADL and quality of life, by modified Barthel Index (mBI) [50,51] and EuroQoL- 5D (EQ-5D) [52]; (iv) cognitive performance, by Stroop Colour Word Test (SCWT) [53], Symbol Digit Modalities Test (SDMT) [54] and Trial Making Test (TMT) [55].

2.4. Instrumental assessment

In addition, the assessment of body composition (t-score, z-score, bone mineral content (BMC), total mass, lean mass, fat mass and fat mass percentage) was performed by means of Dual-Energy X-ray Absorptiometry (DEXA).

2.5. Intervention

All patients deemed eligible and randomized into the two study groups underwent the time assessments described above. The Sid-G patients, in addition to the drug therapy required by their clinical condition, took 1 sachet of SiderAl® Med daily during hospitalization (between T0 and T1) and during the first month of return home (between T1 and T2). During the second month of return home (between T2 and T3), Sid-G patients no longer took the nutritional supplement. The CG patients, on the other hand, continued to take the medication as required by their clinical condition and did not take SiderAL® Med, but were only observed and evaluated at the various points in time in the study.

All patients, regardless of randomization group, underwent intensive rehabilitation treatment between T0 and T1, 2 h per day, 6 days per week. The rehabilitation treatment consisted of activities aimed at improving motor performance, trunk control, walking and autonomy in performing activities of daily living, improving cognitive and speech performance. Thus, the rehabilitation treatment involved a multidisciplinary team consisting of physiotherapists, speech therapists and occupational therapists, while therapists not involved in the rehabilitation treatment carried out the evaluation at the different time points under the study.

2.6. Statistical analysis

As this is a pilot study on a specific subgroup of patients, on whom the actual usefulness of the SiderAL® Med has not yet been studied in the literature, the study was set up as a pilot study. As such, no formal sample sizing was necessary. However, based on Julious' rules (2005) of thumb for clinical pilot studies [56], 12 subjects per group were included for a total population of 24 subjects. The division into the two groups followed a randomization algorithm according to the random sorting procedure. The allocation sequence was generated through PASS2023 software. The sample was described in its clinical and demographic variables using descriptive statistical techniques. Quantitative variables were summarized with mean and standard deviation (SD), and median and interquartile range (IQR) where appropriate. The Shapiro–Wilk probability test was used to assess the normality of the distributions [57]. The within-group analysis was based on the application of the Friedman Test using Bonferroni correction for multiple comparisons for each outcome measure registered at T0, T1, T2 and T3. The between-group analysis was performed using The Mann–Whitney U test to compare the changes from baseline of each outcome for each group, defined as S(T1) - S(T0), where S is one of the outcome measure.

Statistical significance for each test was set at 0.05. Statistical analysis was performed with SPSS 25 (IBM Corp., Armonk, NY, USA).

3. Results

Twenty-four patients, according to inclusion and exclusion criteria, were enrolled in the study. Considering the two groups, Sid-G and CG, both included 12 patients. There are not significant differences between two groups' composition and characteristics, except for EQ-5D ($p = 0.02$) in favour of Sid-G, and SPPB ($p = 0.001$) in favour of CG, as seen in Table 1.

About fatigue, the intra-group analysis showed a statistically significant difference between the four assessment times ($p = 0.0001$) for both groups. Specifically, with regard to the Sid-G between T0 and T1, a statistically significant difference emerged in the motor ($p = 0.002$), cognitive ($p = 0.002$) and psychosocial subscales of fatigue, as well as in total fatigue ($p = 0.002$). Between T1 and T2, significance emerged in motor ($p = 0.009$), cognitive ($p = 0.001$) and in total fatigue ($p = 0.003$). Between T2 and T3, on the other hand, statistical significance is only maintained with regard to total fatigue ($p = 0.016$). As for CG, on the other hand, a statistically significant difference emerged between T0 and T1 with regard to the motor component ($p = 0.002$), the cognitive component ($p = 0.003$) and the psychosocial component ($p = 0.002$), as well as in total fatigue ($p = 0.002$). With regard to the analysis between T1 and T2, the statistically significant difference was only maintained for the motor component ($p = 0.003$) and total fatigue ($p = 0.003$), whereas no statistically significant results emerged in the comparison between T2 and T3 (Table 2).

Intra-group analysis on motor performance, balance and walking showed statistically significant results at all four times ($p = 0.0001$) for both groups. Regarding Sid-G, between T0 and T1, statistically significant results were obtained for the side affected by MI ($p = 0.002$), BBS ($p = 0.002$), SPPB ($p = 0.002$), TUG ($p = 0.002$), AI ($p = 0.002$), FAC ($p = 0.004$), WHS ($p = 0.003$), 6MWT ($p = 0.003$) and 10MWT ($p = 0.008$). Between T1 and T2, statistically significant differences emerged for BBS ($p = 0.002$), WHS ($p = 0.014$) and 6MWT ($p = 0.002$), whereas between T2 and T3, statistically significant differences emerged for TUG ($p = 0.006$), WHS ($p = 0.008$) and 6MWT ($p = 0.004$). As for CG, between T0 and T1 statistically significant results were obtained for MI ($p = 0.002$), TUG ($p = 0.009$), WHS ($p = 0.002$), 6MWT ($p = 0.002$) and 10MWT ($p = 0.012$). Between T1 and T2, statistically significant differences emerged for BBS ($p = 0.001$), SPPB ($p = 0.001$), TUG ($p = 0.001$), WHS ($p = 0.014$) and 6MWT ($p = 0.002$); whereas between T2 and T3, no statistically significant differences emerged for any of the evaluations (Table 2).

Intra-group analysis on cognitive performance, autonomy and quality of life showed statistically significant results at all four times ($p = 0.0001$) for both groups. In particular, for the Sid-G, statistically significant results emerged between T0 and T1 with regard to the execution time of the interference test of the SCWT ($p = 0.002$) and errors at the SCWT ($p = 0.003$), the SDMT ($p = 0.002$) and the TMT ($p = 0.006$). In addition, the results of the total EQ-5D ($p = 0.002$), the VAS component of the EQ-5D ($p = 0.002$) and the mBI ($p = 0.002$) were statistically significant. Between T1 and T2, SCWT interference test time ($p = 0.004$) and errors at SCWT ($p = 0.010$), SDMT ($p = 0.042$), total EQ-5D results ($p = 0.014$), and mBI ($p = 0.002$) were statistically significant. Between T2 and T3 the only statistically significant result was obtained for the errors at SCWT ($p = 0.046$), total EQ-5D results ($p = 0.035$) and VAS component of the EQ-5D ($p = 0.005$). On the other hand, for the CG, statistically significant results emerged between T0 and T1 with regard to the execution time of the SCWT ($p = 0.034$) and errors at the SCWT ($p = 0.002$), the SDMT ($p = 0.009$) and the TMT ($p = 0.050$). Furthermore, the results of the VAS component of the EQ-5D ($p = 0.011$), the VAS component of the EQ-5D (p

Table 1
Clinical and demographic characteristics of the population.

		Sid-G (n = 12)	CG (n = 12)	p value
Gender, W vs M	n	5 vs 7	6 vs 6	p = 0.755
Age, years	Mean ± SD	68.92 ± 14.54	76.60 ± 13.86	p = 0.143
BMI	Mean ± SD	26.23 ± 3.70	26.92 ± 4.77	p = 0.799
MFIS Phy	Median (IQR)	25 (22–27)	23 (21–24)	p = 0.514
MFIS Cog	Median (IQR)	20 (17–23)	23 (20–26)	p = 0.078
MFIS Psy	Median (IQR)	7 (6–7)	6 (4–7)	p = 0.347
MFIS Tot	Median (IQR)	54 (46–55)	52 (50–56)	p = 0.755
MI Affected side	Median (IQR)	58 (58–64)	58 (58–64)	p = 0.590
BBS	Median (IQR)	34 (29–37)	36 (26–38)	p = 0.932
SPPB	Median (IQR)	3 (3–3)	4 (4–5)	**p = 0.001**
AI	Median (IQR)	5 (4–5)	5 (4–5)	p = 0.478
FAC	Median (IQR)	2 (2–3)	2 (1–3)	p = 0.713
WHS	Median (IQR)	3 (2–3)	3 (2–3)	p = 0.671
TUG, seconds	Median (IQR)	27 (20–49)	28 (22–36)	p = 0.630
10MWT, seconds	Median (IQR)	24 (23–31)	26 (22–27)	p = 0.755
6MWT, meters	Median (IQR)	85 (68–106)	100 (84–149)	p = 0.410
SDMT	Median (IQR)	22 (20–31)	16 (12–24)	p = 0.128
TMT B-A	Median (IQR)	23 (16–31)	24 (17–30)	p = 0.755
SCWT, seconds	Median (IQR)	85 (75–128)	87 (74–118)	p = 0.843
SCWT, errors	Median (IQR)	4 (2–6)	7 (4–8)	p = 0.078
EQ-5D	Median (IQR)	15 (11–17)	11 (10–13)	**p = 0.020**
EQ-5D VAS	Median (IQR)	53 (44–56)	45 (26–38)	p = 0.671
mBI	Median (IQR)	36 (26–43)	32 (26–38)	p = 0.630
t-score	Median (IQR)	−1 (–1 – 1)	–1 (–1 – 1)	p = 1.000
z-score	Median (IQR)	0 (–1 – 1)	–1 (–1 – 0)	p = 0.887
BMC	Median (IQR)	2322 (1824–2506)	3420 (1806–4034)	p = 0.457
Fat mass	Median (IQR)	21794 (20602–25242)	26054 (20215–26893)	p = 0.512
Lean mass	Median (IQR)	48736 (35688–55908)	49121 (35681–60561)	p = 0.668
Total mass	Median (IQR)	70670 (63799–79660)	72000 (63504–79496)	p = 0.313
% Fat	Median (IQR)	31 (28–36)	33 (27–37)	p = 0.624

BMI: Body Mass Index; MFIS: Modified Fatigue Impact Scale; Phy: Physical; COG: Cognitive; PSY: Psycosocial; MI: Motricity Index; BBS: Berg Balance Scale; SPPB: Short Physical Performance Battery; AI: Ambulation Index; FAC: Functional Ambulation Category; WHS: Walking Handicap Scale; TUG: Timed Up&Go Test; 10MWT: 10-Metre Walking Test; 6MWT: 6-Minute Walking Test; SDMT: Symbol Digit Modalities Test; TMT: Trial Making Test; SCWT; Stroop Colour Word Test; EQ-5D: EuroQoL-5D; mBI: modified Barthel Index; BMC: Bone Mineral Content.
In bold the statistically significant p-values for $p < 0.05$.

= 0.002) and the mBI (p = 0.002) were statistically significant. No statistically significant results emerged between T1 and T2 and between T2 and T3 (Table 2). With regard to DEXA parameters, the intra-group analysis showed no statistically significant differences for most parameters, with the exception for patients of Sid-G of lean mass (p = 0.017), total mass (p = 0. 032) and fat mass percentage (p = 0.006) between T0 and T1, between T1 and T2 for BMC (p = 0.003), lean mass (p = 0.044), total mass (p = 0.002) and fat mass percentage (p = 0.008). Between T2 and T3, on the other hand, no statistically significant differences were observed in either Sid-G or CG (Table 2).

Changes from baseline in motor (p = 0.007), cognitive (p = 0.0096) and total (p = 0.034) fatigue between T0 and T3 favoured the Sid-G versus the CG (Fig. 1). Specifically, there was a statistically significant improvement between T0 and T1 and between T1 and T2 for motor fatigue ($p < 0.001$ and p = 0.021), cognitive (p = 0.004 and $p < 0.001$) and total fatigue (p = 0.001 and p = 0.048). Between T2 and T3, the statistically significant difference is only maintained for motor fatigue (p = 0.024) (Table 3).

Regarding motor performance, balance and walking, the comparison between the two groups between T0 and T3 showed a statistically significant improvement in BBS ($p < 0.001$), SPPB ($p < 0.001$), AI ($p < 0.001$), FAC (p = 0.017), WHS (p = 0.036), TUG (p = 0.039) and 6MWT ($p < 0.001$) in favour of Sid-G versus CG. In particular, there is a statistically significant improvement in favour of Sid-G between T0 and T1 in BBS (p = 0.001), SPPB (p = <0.001), AI ($p < 0.001$), FAC (p = 0. 017), the WHS (p = 0.017), the TUG (p = 0.012) and the 6MWT (p = 0.033); between T1 and T2 for the BBS ($p < 0.001$), the WHS (p = 0.039), the TUG (p = 0.039) and the 6MWT ($p < 0.001$). Between T2 and T3, the statistically significant difference is only maintained for BBS (p = 0.039) and 6MWT (p = 0.011) (Table 3).

Considering cognitive performance, autonomy and quality of life, the comparison of the two groups between T0 and T3 showed a statistically significant improvement in the SDMT (p = 0.004) and the SCWT time (p = 0.049) in favour of Sid-G patients, compared with CG patients. Between T0 and T1, statistically significant differences emerged between the two groups in favour of Sid-G in SDMT (p = 0.004), the TMT ($p < 0.001$), the SCWT running time ($p < 0.001$), the total EQ-5D (p = 0.039) and the VAS component of the EQ-5D (0.044). Between T1 and T2, on the other hand, statistically significant differences emerged between the two groups with regard to the SDMT (p = 0.048), SCWT execution time ($p < 0.001$), EQ-5D (p = 0.003) and mBI ($p < 0.001$). Between T2 and T3, no statistically significant difference emerged between Sid-G and CG (Table 3). With regard to instrumental assessment, the comparison between Sid-G and CG showed a statistically significant difference between T0 and T3 with regard to BMC (p = 0.005), lean mass (p = 0.005), total mass ($p < 0.001$) and fat mass percentage (p = 0.039). Specifically, BMC was significant between T1 and T2 ($p < 0.001$), whereas between T0 and T1, between T1 and T2 and between T2 and T3, lean mass ($p < 0.001$, p = 0.005, p = 0.001), total mass ($p < 0.001$, p = 0.047) and percentage fat mass (p = 0.015, p = 0.051 and $p < 0.001$) were statistically significant (Table 3).

4. Discussion

Despite the growing interest in the role that vitamins and minerals play in the management of fatigue and motor and cognitive performance [58–60], as far as the authors know, there is no other work in the literature using dietary supplements to counteract post-stroke fatigue. Considering the analyzed data, interesting results emerge from the study. Firstly, the basic hypothesis that nutritional support with SiderAL® Med

Table 2
Intra-group post-hoc analysis between the assessment times in the two groups. P-value significance is assessed at $p < 0.016$ for Bonferroni correction.

	Sid-G			CG		
	p-value T0-T1	p-value T1-T2	p-value T2-T3	p-value T0-T1	p-value T1-T2	p-value T2-T3
Fatigue						
MFIS Phy	**p = 0.002**	**p = 0.009**	**p = 0.021**	**p = 0.002**	**p = 0.023**	p = 0.708
MFIS Cog	**p = 0.002**	**p = 0.001**	p = 0.029	**p = 0.003**	p = 0.317	p = 1.000
MFIS Psy	**p = 0.002**	p = 0.564	p = 0.129	**p = 0.002**	**p = 0.024**	p = 0.317
MFIS Tot	**p = 0.002**	**p = 0.030**	**p = 0.016**	**p = 0.002**	**p = 0.021**	p = 0.582
Motor performance, balance and walking						
MI Affected side	**p = 0.002**	p = 1.000	p = 1.000	**p = 0.002**	p = 1.000	p = 1.000
BBS	**p = 0.002**	**p = 0.002**	p = 0.106	**p = 0.042**	**p = 0.001**	p = 1.000
SPPB	**p = 0.002**	p = 0.435	p = 0.722	**p = 0.026**	p = 0.001	p = 1.000
AI	**p = 0.002**	p = 1.000	p = 1.000	**p = 0.002**	**p = 0.023**	p = 1.000
FAC	**p = 0.004**	p = 1.000	p = 1.000	p = 0.429	p = 1.000	p = 1.000
WHS	**p = 0.003**	**p = 0.014**	**p = 0.008**	**p = 0.005**	p = 1.000	p = 1.000
TUG, seconds	**p = 0.002**	p = 0.754	**p = 0.006**	**p = 0.009**	**p = 0.001**	p = 0.194
10MWT, seconds	**p = 0.008**	p = 0.049	p = 0.714	**p = 0.012**	p = 0.078	p = 0.127
6MWT, meters	**p = 0.003**	**p = 0.002**	**p = 0.004**	**p = 0.002**	**p = 0.002**	p = 0.072
Cognitive performance, autonomy and quality of life						
SDMT	**p = 0.002**	**p = 0.042**	p = 0.098	**p = 0.009**	p = 0.084	p = 0.192
TMT B-A	**p = 0.006**	p = 0.121	p = 0.143	**p = 0.050**	p = 1.000	p = 1.000
SCWT, seconds	**p = 0.002**	**p = 0.004**	p = 0.094	**p = 0.034**	p = 0.750	p = 1.000
SCWT, errors	**p = 0.003**	**p = 0.010**	**p = 0.046**	**p = 0.002**	p = 0.015	p = 0.317
EQ-5D	**p = 0.002**	**p = 0.014**	**p = 0.035**	**p = 0.011**	p = 0.317	p = 0.317
EQ-5D VAS	**p = 0.002**	p = 0.100	**p = 0.005**	**p = 0.002**	p = 0.317	p = 1.000
mBI	**p = 0.002**	**p = 0.002**	p = 0.068	**p = 0.002**	p = 0.317	p = 0.317
DEXA						
t-score	p = 0.134	p = 0.242	p = 0.341	p = 0.001	p = 1.000	p = 1.000
z-score	p = 0.106	p = 0.117	p = 0.812	p = 0.653	p = 1.000	p = 1.000
BMC	p = 0.691	**p = 0.003**	p = 0.188	p = 0.859	p = 1.000	p = 1.000
Fat mass	p = 0.245	p = 0.350	p = 0.226	p = 0.414	p = 1.000	p = 1.000
Lean mass	**p = 0.017**	**p = 0.044**	p = 0.126	p = 0.328	p = 1.000	p = 1.000
Total mass	**p = 0.032**	**p = 0.002**	p = 0.261	p = 0.414	p = 1.000	p = 1.000
% Fat	**p = 0.006**	**p = 0.008**	p = 0.351	p = 0.918	p = 1.000	p = 1.000

BMI: Body Mass Index; MFIS: Modified Fatigue Impact Scale; Phy: Physical; COG: Cognitive; PSY: Psycosocial; MI: Motricity Index; BBS: Berg Balance Scale; SPPB: Short Physical Performance Battery; AI: Ambulation Index; FAC: Functional Ambulation Category; WHS: Walking Handicap Scale; TUG: Timed Up&Go Test; 10MWT: 10-Metre Walking Test; 6MWT: 6-Minute Walking Test; SDMT: Symbol Digit Modalities Test; TMT: Trial Making Test; SCWT; Stroop Colour Word Test; EQ-5D: EuroQoL-5D; mBI: modified Barthel Index; BMC: Bone Mineral Content.
In bold the statistically significant p-values for $p < 0.05$.

supplementation could somehow positively influence fatigue in older adults with stroke outcomes was fulfilled. In the first month, in which all patients underwent the rehabilitation treatment, all patients included in the study showed a significant improvement. In particular, the Sid-G patients, who also took the nutritional supplementation, showed a significant improvement in all clinical scales, as well as in some instrumental parameters. In particular, the patients showed an increase in lean and total mass and a decrease in the percentage of fat mass. The CG patients also showed an improvement at the end of the first month in almost all examined parameters, with the exception of the DEXA parameters. In the second month, when the patients were no longer under intensive rehabilitation treatment, the Sid-G patients (who nevertheless continued to take the dietary supplement) showed a significant improvement in fatigue in all components, except psychosocial fatigue. There was also an improvement in balance, walking and functional capacity, as well as in the speed of information processing, cognitive interference management and perceived quality of life. Lean and total mass also improved significantly and the percentage of fat mass decreased significantly. In CG patients, on the other hand, there was a significant improvement in fatigue in all of its components, with the exception of cognitive fatigue, balance, walking and functional capacity; while no significant results emerged with regard to cognitive performance, quality of life and autonomy. In addition, there were no significant changes in body composition. At the third month, during which nutritional supplementation with SiderAL® Med was discontinued, Sid-G patients showed significant improvement only in the motor component of fatigue and total tiredness, dynamic balance, walking and functional capacity, and perceived quality of life.

When comparing the improvements between the two groups, it was found that throughout the study period, patients taking the dietary supplement with SiderAL® Med showed a significant decrease in motor, cognitive and total fatigue, which was most noticeable during the two months of taking the dietary supplement. Interestingly, the Sid-G patients also showed a significant decrease in motor fatigue in the follow-up month during which they were no longer taking SiderAL® Med. Considering motor performance, interesting results emerged: in fact, the two groups showed a significant difference in the improvement of balance, which was maintained throughout the study period, as well as the improvement of functional capacity. The results also suggest that nutritional supplementation with SiderAL® Med may also have a positive impact on cognitive performance, particularly on information processing speed and attention. Also interesting are the results obtained from the instrumental assessment of the body component: indeed, it was found that throughout the study period there was a significant decrease in the percentage of fat mass, as well as a significant increase in lean mass and total mass. Interestingly, a change in BMC occurred in the second month of taking SiderAL® Med.

It is known in the literature that an inadequate intake of vitamins and minerals can be associated with physical fatigue, lack of energy or lethargy, as well as cognitive dysfunctions [61]. The supplementation of vitamins (A, B1, B2, B6, B12, C, D, E, K) and minerals, such as magnesium and iron, can counteract fatigue and lead to an improvement not only in physical performance but also in cognitive performance. It is known, in fact, that an iron supplement can improve attention, memory and learning, in young women who have iron deficiency but not anaemia [61,62].

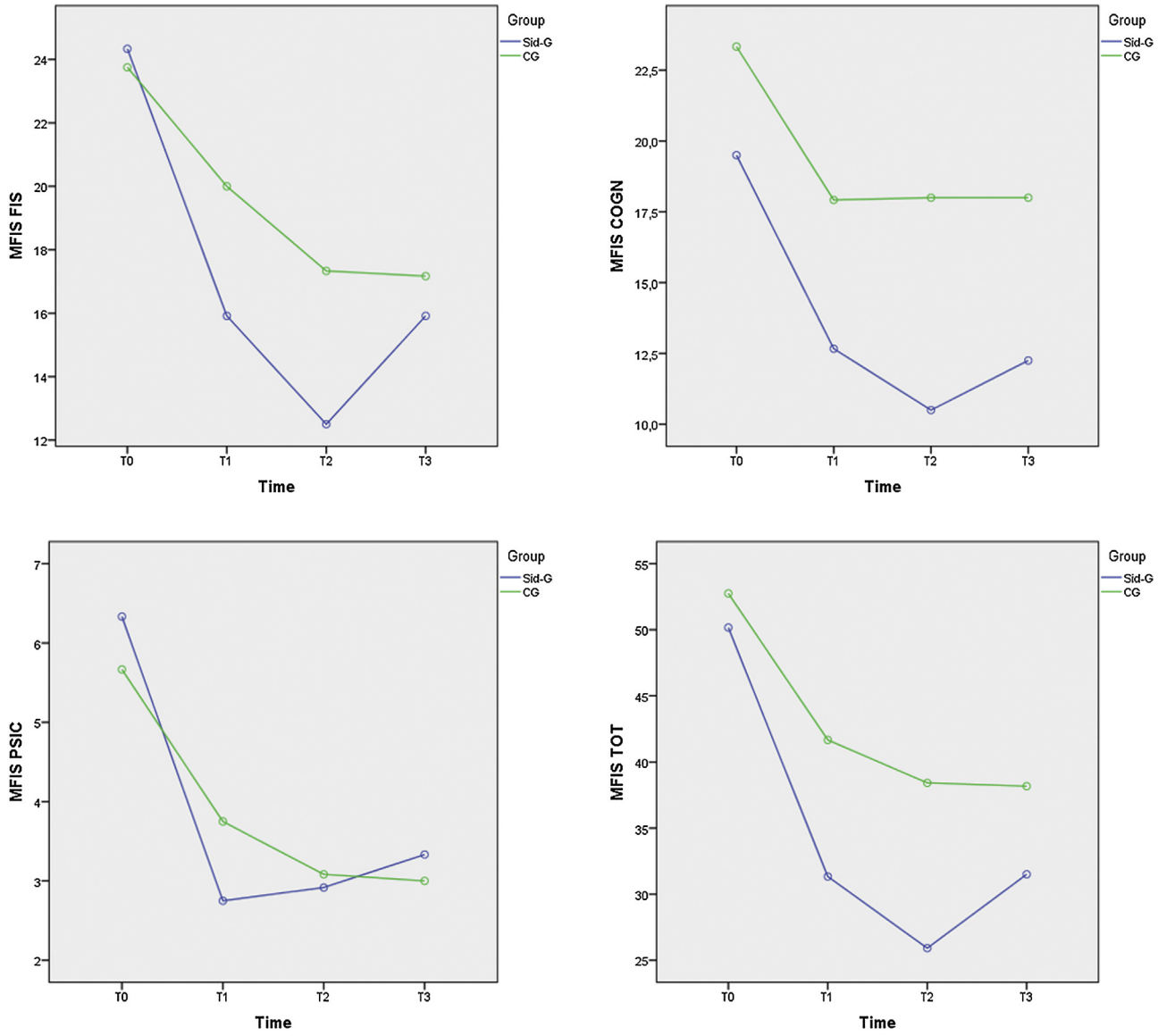

Fig. 1. Trend of motor, cognitive, psychosocial and total fatigue in the two groups between T0 and T3.

Some authors have emphasised the close relationship between fatigue and vitamins and minerals supplementation; how the effects they produce at a cellular level then translate at a systemic level into an improvement in fatigue, both motor and cognitive, and an improvement in motor and physical performance [63], confirming the results obtained in this study. It is therefore possible to hypothesise that the steady improvement in fatigue, especially motor fatigue, is attributable to the change in body composition and the increase in mobility and functional capacity, i.e. that by improving the nutritional aspect and lean mass, the patients were also able to achieve, through rehabilitation therapy, an improvement in motor performance and consequently a better management of fatigue. This could have established a 'virtuous circle': improved nutritional intake, reduced motor and cognitive fatigue, increased motor and cognitive functions, increased movement and social interactions, improved quality of life, improved muscular function, reduced motor and cognitive fatigue, improved motor and cognitive performance, and so on.

What emerged from the study could be easily integrated into clinical practice. Having evaluated the positive and statistically significant effect of the association between nutritional supplementation and rehabilitation, SiderAL® Med could be considered as an adjunct to rehabilitation treatment. Indeed, by reducing the effects of post-stroke fatigue, it could emphasize the effects of rehabilitation, promoting its effects and improving its outcome.

The study has some limitations. One of them is definitely the sample size; however, since the relationship between SiderAL® Med and post-stroke fatigue has never been investigated, this study was set up as a pilot study. For this reason, it was not deemed necessary to make a formal sample size estimate, but based on Julious ' rules of thumb for pilot clinical trials [56], 12 patients per group were included, for a total of 24 patients. In addition, for phase 2 rehabilitation pilot studies, the guidelines identify an initial convenience sample of at least six participants [64]. Another limitation of the study is the lack of a double blind. In fact, in this study, blinding was considered appropriate for the personnel involved in patient selection, randomization, assessments, treatment, and statistical analysis, but not for the patient. However, it is believed that the presence of these blinded figures did not produce selection or reporting bias.

For these reasons, future research should not only be designed to apply the blind to patients as well, but also consider a larger sample size. To corroborate this, a clinical trial is currently underway that, taking into account the results obtained so far, has included a larger number of patients. Moreover, we are going to include in the clinical trial biochemical and bioimpedance analysis to more accurately identify not only changes that can be objectified with rating scales, but also

Table 3
Inter-group analysis for all evaluation times.

	T0 Median (IQR)	T1 Median (IQR)	T2 Median (IQR)	T3 Median (IQR)	p value T0-T3	p value T0-T1	p value T1-T2	p value T2-T3
Fatigue								
MFIS Phy					**p = 0.007**	**p < 0.001**	**p = 0.021**	**p = 0.024**
Sid-G	25 (22–27)	17 (13–19)	13 (11–15)	16 (11–21)				
CG	23 (21–24)	20 (17–22)	18 (14–19)	17 (14–20)				
MFIS Cog					**p = 0.009**	**p = 0.004**	**p < 0.001**	p = 0.089
Sid-G	20 (17–23)	14 (10–16)	11 (8–13)	13 (10–14)				
CG	23 (20–26)	19 (14–21)	18 (14–21)	18 (14–21)				
MFIS Psy					p = 0.378	p = 0.062	p = 0.078	p = 0.219
Sid-G	7 (6–7)	3 (2–4)	3 (2–4)	3 (2–4)				
CG	6 (4–7)	4 (2–5)	3 (2–4)	3 (2–4)				
MFIS Tot					**p = 0.034**	**p = 0.001**	**p = 0.048**	p = 0.072
Sid-G	54 (46–55)	34 (28–36)	28 (24–30)	30 (27–40)				
CG	52 (50–56)	40 (33–46)	39 (29–42)	37 (30–43)				
Motor performance, balance and walking								
MI Affected side					p = 0.514	p = 0.514	p = 1.000	p = 1.000
Sid-G	58 (58–64)	88 (76–100)	88 (76 –100)	88 (76 –100)				
CG	58 (58–64)	100 (84–100)	100 (84–100)	100 (84–100)				
BBS					**p < 0.001**	**p = 0.001**	**p < 0.001**	**p = 0.039**
Sid-G	34 (29–37)	45 (43–48)	51 (49–53)	53 (50–56)				
CG	36 (26–38)	41 (28–48)	39 (26–46)	39 (26–46)				
SPPB					**p < 0.001**	**p < 0.001**	p = 0.089	p = 0.514
Sid-G	3 (3–3)	8 (8–9)	8 (7–9)	8 (7–9)				
CG	4 (4–5)	7 (3–7)	6 (2–6)	6 (2–6)				
AI					**p < 0.001**	**p < 0.001**	p = 1.000	p = 1.000
Sid-G	5 (4–5)	3 (2–3)	3 (2–3)	3 (2–3)				
CG	5 (4–5)	4 (3–4)	4 (3–4)	4 (3–4)				
FAC					**p = 0.017**	**p = 0.017**	p = 1.000	p = 1.000
Sid-G	2 (2–3)	3 (3–4)	3 (3–4)	3 (3–4)				
CG	2 (1–3)	3 (1–3)	3 (1–3)	3 (1–3)				
WHS					**p = 0.036**	**p = 0.017**	**p = 0.039**	p = 0.101
Sid-G	3 (2–3)	5 (4–5)	5 (5–5)	5 (5–5)				
CG	3 (2–3)	4 (3–4)	4 (3–4)	4 (3–4)				
TUG					**p = 0.039**	**p = 0.012**	**p = 0.039**	p = 0.068
Sid-G	27 (20–49)	20 (10–33)	19 (13–31)	22 (14–37)				
CG	28 (22–36)	26 (18–31)	28 (22–34)	29 (23–33)				
10MWT					p = 0.551	p = 1.000	p = 0.410	p = 1.000
Sid-G	24 (23–31)	18 (16–23)	14 (12–17)	16 (15–19)				
CG	26 (22–27)	17 (17–19)	16 (13–17)	18 (16–19)				
6MWT					**p < 0.001**	**p = 0.033**	**p < 0.001**	**p = 0.011**
Sid-G	85 (68–106)	175 (138–218)	245 (205 –290)	245 (198–275)				
CG	100 (84–149)	150 (149–190)	140 (130–170)	130 (110–150)				
Cognitive performance, autonomy and quality of life								
SDMT					**p = 0.004**	**p = 0.004**	**p = 0.048**	p = 0.075
Sid-G	22 (20–31)	33 (28–40)	30 (26–38)	31 (26–38)				
CG	16 (12–24)	26 (19–35)	25 (17–32)	24 (17–32)				
TMT B-A					p = 0.671	**p < 0.001**	p = 0.378	p = 0.942
Sid-G	23 (16–31)	27 (19–44)	14 (13–35)	11 (10–32)				
CG	24 (17–30)	71 (49–96)	18 (13–31)	19 (14–32)				
SCWT, time					**p = 0.049**	**p < 0.001**	**p < 0.001**	p = 0.098
Sid-G	85 (75–128)	75 (62–94)	68 (55–87)	66 (54–85)				
CG	87 (74–118)	79 (67–93)	76 (65–91)	76 (64–91)				
SCWT, errors					p = 0.319	p = 0.178	p = 0.590	p = 0.378
Sid-G	4 (2–6)	1 (0–2)	0 (0–1)	0 (0–0)				
CG	7 (4–8)	2 (2–4)	1 (1–2)	1 (1–2)				
EQ-5D					p = 0.242	**p = 0.039**	**p = 0.003**	p = 0.128
Sid-G	15 (11–17)	9 (7–11)	8 (6–10)	10 (8–12)				
CG	11 (10–13)	8 (7–10)	8 (7–9)	8 (7–9)				
EQ-5D VAS					p = 0.590	**p = 0.044**	p = 0.242	p = 0.241
Sid-G	53 (44–56)	80 (70–81)	78 (75–83)	70 (65–75)				

(continued on next page)

Table 3 ***(continued)***

	T0 Median (IQR)	T1 Median (IQR)	T2 Median (IQR)	T3 Median (IQR)	p value T0-T3	p value T0-T1	p value T1-T2	p value T2-T3
CG	45 (26–38)	73 (59–80)	73 (59–80)	73 (59–80)				
mBI					p = 0.219	p = 0.478	**p < 0.001**	p = 0.347
Sid-G	36 (26–43)	79 (66–85)	91 (84–96)	95 (89–100)				
CG	32 (26–38)	73 (59–80)	84 (72–86)	84 (74–86)				
DEXA								
t-score					p = 0.059	p = 0.193	p = 0.751	p = 0.327
Sid-G	–1 (–1 – 1)	–1 (–1 – 1)	–1 (–1 – 1)	0 (–1 – 1)				
CG	–1 (–1 – 1)	–1 (–1 – 1)	–1 (–1 – 1)	–1 (–1 – 1)				
z-score					p = 0.425	p = 0.507	p = 0.468	p = 0.116
Sid-G	0 (–1 – 1)	0 (–1 – 1)	0 (–1 – 1)	0 (–1 – 1)				
CG	–1 (–1 – 0)	–1 (–1 – 0)	–1 (–1 – 0)	–1 (–1 – 0)				
BMC					**p = 0.005**	p = 0.178	**p < 0.001**	p = 0.445
Sid-G	2322 (1824–2506)	2334 (1877–2447)	2497 (1877–2567)	2220 (1723–2442)				
CG	3420 (1806–4034)	3420 (2806–4036)	3440 (1817–4154)	3416 (2800–4046)				
Fat mass					p = 0.689	p = 0.954	p = 0.795	p = 0. 751
Sid-G	21794 (20602–25242)	21478 (20602–25242)	21690 (17978–24523)	21967 (17255–24956)				
CG	26054 (20215–26893)	26054 (20215–26893)	26052 (20219–26874)	26054 (20215–26893)				
Lean mass					**p = 0.005**	**p < 0.001**	**p = 0.005**	**p = 0.001**
Sid-G	48736 (35688–55908)	50130 (37525–57746)	50508 (37028–57248)	52154 (37647–57868)				
CG	49121 (35681–60561)	48121 (34680–60448)	48049 (35649–59887)	48144 (36482–58993)				
Total mass					**p < 0.001**	**p < 0.001**	**p < 0.001**	**p = 0.047**
Sid-G	70670 (63799–79660)	72614 (65466–81644)	73936 (65985–82987)	74794 (65885–82843)				
CG	72000 (63504–79496)	71927 (62500–74491)	71928 (62542–74571)	72145 (63384–79179)				
% Fat					**p = 0.039**	**p = 0.015**	**p = 0.051**	**p < 0.001**
Sid-G	31 (28–36)	28 (26–34)	27 (25–36)	27 (25–36)				
CG	33 (27–37)	32 (27–35)	34 (28–37)	34 (27–39)				

BBMI: Body Mass Index; MFIS: Modified Fatigue Impact Scale; Phy: Physical; COG: Cognitive; PSY: Psycosocial; MI: Motricity Index; BBS: Berg Balance Scale; SPPB: Short Physical Performance Battery; AI: Ambulation Index; FAC: Functional Ambulation Category; WHS: Walking Handicap Scale; TUG: Timed Up&Go Test; 10MWT: 10-Metre Walking Test; 6MWT: 6-Minute Walking Test; SDMT: Symbol Digit Modalities Test; TMT: Trial Making Test; SCWT; Stroop Colour Word Test; EQ-5D: EuroQoL-5D; mBI: modified Barthel Index; BMC: Bone Mineral Content.
In bold the statistically significant p-values for $p < 0.05$.

modifications at the biochemical level. In addition, it would also be interesting to evaluate the effects of SiderAL® Med on other categories of patients, in whom fatigue determines a significant impact on motor and cognitive performance and quality of life.

5. Conclusion

In conclusion, nutritional supplementation with SiderAL® Med, in concert with intensive rehabilitation treatment, appears to be effective in the management of fatigue and in improving motor and cognitive performance and quality of life, representing a valuable tool to associate with rehabilitation treatment in stroke patients.

Funding

None to declare.

Conflict of interest

None.

Acknowledgements

Authors would like to thank Dr. Germano Tarantino e Dr. Maria Sole Rossato (Pharmanutra S.p.A.) for their technical support.

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