

Dietary Intake and Intervention in Chronic Stroke: Review of the Evidence

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Abstract

Despite evidence for a role of nutrition in the development of metabolic dysfunction, physical deconditioning, and psychological dysfunction common post-stroke, very little is known about the dietary habits and nutritional needs of chronic (>6 months) stroke survivors. This review summarizes the available evidence regarding dietary intake adequacy in chronic stroke survivors. It appears that a combination of screening methods, including food record, laboratory and malnutrition screening tools assessments may be beneficial to assess the dietary intake adequacy of stroke survivors. We also review the evidence suggesting the need for dietary modification by summarizing the strongest evidence (i.e., randomized controlled trial data) supporting and refuting the impact of nutritional interventions on clinical outcomes post-stroke. Data suggest that the B vitamins, omega 3s and vitamin D have promising effects on recovery post-stroke; however, to date, study limitations make drawing definitive conclusions regarding the impact of nutritional supplementation difficult. Further research is needed to provide insight on the ideal supplement dose and duration and about how different rehabilitation therapies (i.e., nutritional supplements, medications, exercise and caloric restriction) may interact to affect recovery. A better understanding of the role of nutrition during chronic stroke is needed as this information may one day help to individualize rehabilitation approaches to optimize patient outcomes.

Keywords: Chronic stroke; Nutrition; Recovery

Introduction

While there is evidence that common consequences of a stroke (i.e., difficulty eating and changes to the desire to eat) may negatively affect dietary intake and health outcomes in the acute phase of stroke [1], less is known about the long-term effects of stroke on dietary intake and the nutritional status in chronic (>6 months) stroke survivors. Further, the majority of research in stroke survivors has focused on increasing physical activity following a stroke [2], with little investigation on the benefits of altering dietary habits, despite evidence for a role of nutrition in the development of metabolic dysfunction, physical deconditioning, and psychological dysfunction common post-stroke [3-5]. Therefore, this review summarizes the available evidence regarding dietary intake adequacy in chronic stroke survivors. We also review the evidence suggesting the need for dietary modification by summarizing the impact of nutritional interventions on clinical outcomes post-stroke.

Evidence of dietary intake adequacy in chronic stroke

Weighted food records are often considered the gold standard among dietary intake assessments because they do not rely on respondents' memory and are open-ended. However, because the recording of dietary intake during chronic stroke may be hindered (i.e., post-stroke cognitive impairments and apraxia) [6], various additional methods (i.e., clinical laboratory analyses and nutritional risk screening assessments) for assessing nutritional risk may be necessary. This section reviews the current evidence available to assess the adequacy of dietary intake in chronic stroke.

Dietary intake adequacy by food records

In stroke survivors at least six months post-stroke, energy intakes of $1,503 \pm 504$ kcal/day (mean \pm SD) for women and $1,904 \pm 550$ kcal/day for men are reported, which is ~80% of the recommended Estimated Average Requirement (EAR) values for energy [7]. The EAR is the intake level for a nutrient at which the needs of 50% of the population are met. This study also reports a trend for those living with a care giver to receive a lower percentage of the EAR for energy intake (75%) compared to living in institutions (85%) or with non-residential support (96%).

Protein intakes of 62.8 ± 18.9 g/day for women and 64.2 ± 15.6 g/day for men also are reported, which is ~160% of EAR values for protein [7]. However, the biological value, a measure of the proportion of absorbed protein from a food which becomes incorporated into the proteins of the organism's body, of the protein intake is not reported. Similar results for both energy and protein are observed in another studies six months post-stroke [8]; however, to the extent of our awareness, food record data beyond six months is not reported in the literature. Further, micronutrient intakes are unreported from food records during chronic stroke.

Nutritional risk by clinical assessment tools

We have previously used clinical laboratory assessment as a surrogate indicator of nutritional risk, generally finding that albumin (indicator of protein intake status) and hemoglobin (indicator of iron and B vitamin intake status) are 5–10% lower and lipids (indicator of the amount and type of dietary fat and refined carbohydrate intake) more favorable in chronic stroke (~4 years stroke latency) than age matched non-stroke adults using the National Health and Nutrition Examination Survey (NHANES) data [9]. The lower albumin and hemoglobin concentration suggest that either protein and iron needs

are elevated or dietary intake of protein and iron are reduced following a stroke, respectively. However, <10% of stroke survivors were at nutritional risk based upon a low albumin (<3.5 g/dL), while ~50% had low hemoglobin (<14 g/dL for males and <12 g/dL for females). Additionally, it must be noted that greater lipid medication usage likely explains the lower lipid profiles in stroke survivors.

Other clinical laboratory reports suggest deficiencies in micronutrients in chronic stroke. In the NHANES cohort, 71% of stroke survivors are found to be deficient (25(OH)D<30 ng/dL) in vitamin D [10]. Further, insufficient folate, vitamins B6 and B12 levels are associated with increased levels of homocysteine and methylmalonic acid (MMA), thus homocysteine and MMA are surrogate markers of B vitamin deficiency. Using the following cutpoints to indicate elevated values, $\geq 15 \mu\text{mol/L}$ for homocysteine and $\geq 0.37 \mu\text{mol/L}$ for MMA, 34% of stroke survivors (~1.5 years post-stroke) have elevated homocysteine and/or MMA [5]. These data indicate that chronic stroke survivors may be at risk for several micronutrient deficiencies.

Using nutritional risk screening assessment tools, such as the subjective global assessment (SGA) [11] and Mini Nutritional Assessment (MNA) [12] there is evidence that 11% of stroke survivors are considered malnourished at 16-18 months [13,14], with limited data beyond the first two years post-stroke. Further, ~45% of stroke survivors lose >3 kg of body weight within the first 16 months after their stroke onset [14]. However, overweight and obesity are prevalent in ~65% of chronic stroke survivors [15] and impaired glucose tolerance and type 2 diabetes mellitus (T2DM) in ~80% [16], indicating that following this initial weight loss caloric intake exceeding expenditure in stroke survivors.

Together, these data indicate that more research is needed to fully understand how chronic stroke impacts dietary intake and nutritional requirements. This information would be useful in the development of rehabilitation guidelines to prevent the development of malnutrition and chronic disease and disability and promote optimal recovery post-stroke.

Evidence suggesting the need for dietary modification in stroke

This section reviews the current evidence surrounding the effects of dietary modification (i.e., oral intake retraining and altering dining conditions) on nutrient intake and clinical outcomes. A comprehensive literature search also was conducted using the PubMed database (National Library of Medicine, Bethesda, MD) inclusively through May 31, 2017 on randomized controlled nutritional supplementation trials using the keywords: stroke survivor, stroke history, stroke patient, rehabilitation, supplementation, nutritional intake, and diet. Relevant study details are presented in Table 1. Briefly, a total of 11 trials were identified which specifically examined the effects of dietary supplementation on secondary prevention, physical functioning, fracture risk, subjective outcomes, and cognitive function. Study sample sizes ranged from 11 to 18,645 individuals, and the follow-up duration ranged from 1.6 months to 7.2 years.

Oral intake retraining and alteration of dining conditions

In those with eating difficulties post-stroke, multidisciplinary care appears necessary to ensure proper nutritional education, an adequate dining environment, dysphagia training, oral care, feeding and possible tube feeding skills [17]. Specific recommendations for the use of tube

feeding in chronic stroke is reviewed extensively in previous publications [18,19]; thus, are not explored in this current review. In tube fed stroke survivors fed solely through enteral feedings, nutritional status (i.e., albumin, pre-albumin, total cholesterol, hemoglobin, BMI, arm circumference and skin fold) gradually improves from the time of stroke through 12 months post [20]; hence, tube feeding appears effective for improving nutritional status. However, previous studies suggest that long-term tube-feeding may develop hypoalbuminemia despite being provided sufficient calories [21], suggesting the importance of encouraging oral nutrition when possible.

Studies show that it is possible to retrain chronic stroke survivors with eating problems to eat [22,23]. In a case report, a 78 year old man who was dependent upon tube feedings (due to dysphagia) since his stroke three years prior, participated in a rehabilitation study aimed at training him to swallow [22]. At baseline, the patient reported that he had lost hope in finding a treatment. After 10 weeks of training, he was able to drink liquids and after 20 additional weeks of training, he was able to comfortably eat solid foods. Additionally, prior to beginning the training, this patient required help with bathing, washing, dressing and eating; however, after the training, the patient only required assistance with bathing and tying his shoes. These observations highlight the importance of periodic monitoring of those dependent on long-term tube feedings as they suggest that improvements in other activities of daily living may parallel achievement of eating autonomy. The review of the various methods available to retain eating is beyond the scope of this current manuscript, but other summative publications exist [24,25].

It is suggested that 66% of the causes of poor dietary consumption are modifiable (i.e., poor dining environment, limited menu choices and restrictive diets). In a study of older residents at a nursing home (40% were chronic stroke survivors) served a buffet-style meal one time per day for three months, a 52% increase in resident satisfaction was observed. However, the alteration in the meal style did not result in changes in body weight or biochemical indices of nutrition (i.e., hemoglobin, hematocrit, cholesterol and prealbumin) [26]. Other studies addressing foodservice style in nursing homes show a 25% increase in energy and protein intakes, as well as significant increases in blood folate, serum creatinine, and retinol [27]. While promising, these data indicate that more research is needed to definitively understand how altering dining conditions during chronic stroke can promote nutrient intake.

Secondary stroke prevention

Risk for recurrent stroke is six times greater than the first stroke [28], indicating the importance of secondary stroke prevention. This section reviews the available evidence for how altering dietary intake through behaviour change and nutritional supplementation reduces the risk of stroke recurrence.

Behavior change

To date, nutritional interventions related to secondary prevention mainly focus on empowering individuals to alter modifiable risk factors for chronic disease, including hypertension, hypercholesterolemia, and excessive alcohol intake. In a behavioral intervention study, stroke survivors (1-9 years post-stroke) completed two 2 h group sessions per week for nine weeks with one hour focused on education (behavior change, including managing stroke complications, nutrition, diet and review of stroke risk factors) and 1 h

for moderate intensity exercise (combination of aerobic fitness, strength, mobility and balance exercise) [29]. 42% of participants reduced their waist circumference, 72% reduced fiber and fat intake and 67% reduced salt intake. Additionally, timed up and go scores decreased 3.89 s and quality of life scores increased by 7%. These effects were maintained throughout a 3 month follow-up period. Similar results are observed in a low income, urban African American stroke population following a health promotion program that consisted of three days per week for 12 weeks [30]. Participants participated in classes focused on nutrition education and health behavior and an exercise intervention consisting of aerobic and strength exercise and flexibility lasting between 45-70 min. Body weight decreased 2.8 lbs, total cholesterol decreased 6% and Rate Your Plate scores, a questionnaire used to assess fat intake, increased 12%. Quality of life and depression scores also improved. To date, there are no studies available examining the impact of purposeful weight reduction on outcomes after stroke; however, these data indicate programs that incorporate exercise and education with nutrition modification may encourage health promotion, reducing the risk for stroke recurrence.

B vitamin supplementation and cardiovascular risk

Hyperhomocysteinemia is associated with greater cardiovascular disease risk [31]. Homocysteine can mediate the formation of cardiovascular disease by several different mechanisms including increased proliferation of vascular smooth muscle cells, endothelial dysfunction, oxidative damage, and collagen synthesis. Treatment with B vitamins may reduce homocysteine by ~30% in stroke survivors [32] and reduce the risk of overall stroke in participants with known cardiovascular disease [33,34]. However, numerous factors may modulate the impact of B vitamins on cardiovascular risk in stroke survivors.

In the HOPE 2 trial, which supplemented adults with known cardiovascular disease (9% with a history of stroke) daily with 2.5 mg of folic acid, 50 mg of vitamin B6 and 1 mg of vitamin B12 versus a placebo for 5 years, supplementation resulted in 24% reduced risk for overall stroke, but not stroke severity or disability [33]. A larger treatment benefit was observed in those that were younger (<69 years), from countries without folic acid fortification of grains, and individuals with higher baseline homocysteine and cholesterol levels and those not receiving antiplatelet or lipid lowering drugs at enrollment. Conversely, in the VISP study, vitamin B supplementation at higher doses (2.5 mg folic acid, 25 mg vitamin B6 and 0.4 mg vitamin B12 daily) for up to 24 months resulted in a reduced recurrent vascular risk in stroke survivors compared to lower doses (20 µg folic acid, 0.2 mg vitamin B6 and 6 µg vitamin B12), but only those >67 years old [34]. The VISP study controlled for cardiovascular disease severity, B12 status, renal function and antiplatelet use not controlled for in the HOPE 2 trial, which many explain the variation in findings. When examining the effects of high dose B vitamin specifically in those using antiplatelet therapy, the results of the VISP study suggest that the risk for recurrent stroke may actually be higher among stroke survivors taking antiplatelet therapy [35]. The suggestion that antiplatelet therapy modifies the potential benefit of B vitamin supplementation is corroborated by the VITATOPS study, which consisted of supplementing stroke and transient ischemic attack survivors with 2 mg folic acid, 25 mg vitamin B6 and 0.5 mg vitamin B12 for a median of 3.4 years. This study suggests a positive effect of B vitamins on subsequent stroke, myocardial infarction or death from vascular causes, but only in those not taking antiplatelet drugs at

baseline [36]. After six months of supplementation it also was observed that B vitamins did not reduce blood concentrations of biomarkers of inflammation (C-reactive protein, interleukin-6 and soluble CD40L, endothelial dysfunction (vascular cell adhesion molecule-1 and intracellular cell adhesion molecule-1) or hypercoagulability (soluble P-selectin, prothrombin fragment 1 and 2 and D-dimer), despite significant reductions in homocysteine [37]. Further, after at least two years of supplementation, it was observed that carotid intima-medial thickness and flow-mediated dilation did not improve [38], nor did the progression of brain lesions [39]. Overall, a meta-analysis including these three studies (HOPE 2, VISP and VITATOPS) found that homocysteine lowering with B vitamins is related to a significant reduction (29%) in overall stroke risk, but only among those with high vascular risk who are not taking antiplatelet therapy [40].

The SU.FOL.OM3 trial examined the combined effects of B vitamin and omega 3 supplementation on secondary risk prevention. Subjects with a cardiovascular disease history (myocardial infarction (46%), unstable angina (29%) or ischemic stroke (25%)) within the preceding 12 months were randomized to one of four groups: 1) 0.56 mg 5-methyltetrahydrofolate (predominant form of folate in circulation), 3 mg vitamin B6, and 0.02 mg vitamin B12; 2) 600 mg of omega 3s (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a 2:1 ratio); 3) B vitamins plus omega 3s; or 4) placebo [41]. The authors observe that those receiving B vitamins have a 46% reduction in the risk of ischemic stroke, but omega 3s have no significant effects on any major cardiovascular event during the 4.7 year median follow up. These data suggest that further research is needed to determine which populations of individuals at cardiovascular risk may have the greatest benefit of B vitamin supplementation on future events.

Omega 3 supplementations and cardiovascular risk

In addition to the SU.FOL.OM3 study, other studies have examined the effects on omega 3s on secondary prevention in stroke survivors due to the positive effects in non-stroke populations, including decreased arrhythmias, lower triglycerides, lower blood pressure, and decreased platelet aggregation [41] and findings from SU.FOL.OM3 that baseline plasma fatty acid profiles are inversely associated with recurrence of cardiovascular diseases [42]. However, similar to the SU.FOL.OM3 trial, the results of supplementation studies do not appear supportive in stroke survivors. An early study by Green et al. [43] found no effect on cholesterol fraction or platelet function following a small daily dose of EPA (1.8 g) for six weeks in subjects with previous stroke or transient ischemic attacks. Similarly, in survivors >3 months post stroke, a 12 week supplementation of 3 g of fish oil (300 mg EPA and 700 mg DHA) per day did not result in significant effects on serum lipids, inflammation, or hemostatic markers [44]. Conversely, in the JELIS trial [45], which examined the additive effects of 1800 mg EPA to statin therapy, stroke survivors supplemented daily for around five years showed a 20% relative reduction in recurrent stroke compared to statin therapy alone. Interestingly, in non-stroke populations, studies have found that fish oil and/or omega 3 supplementation is associated with lower rate of cardiovascular mortality, but not stroke risk [46,47].

Vitamin D supplementation and cardiovascular risk

Vitamin D3, cholecalciferol, the naturally occurring form of vitamin D is produced by the human body when skin makes contact with direct sunlight, while vitamin D2, ergocalciferol, is plant derived and the form found in most vitamin D supplements. To the best of our

knowledge, only one placebo controlled study has examined the effects of vitamin D supplementation on vascular health in stroke survivors. Witham et al. [48] supplemented community dwelling patients with a history of stroke and baseline 25-hydroxyvitamin D levels <75 nmol/L with 100,000 IU vitamin D₂ to examine the effects on vascular risk. No differences were observed on blood pressure or flow mediated dilatation following 16 weeks of supplementation despite early differences in flow mediated dilatation at the 8 week time point. However, more research is needed to verify the lack of an effect of vitamin D on vascular health post-stroke.

Physical functioning

Hemiplegia, paralysis of one side of the body, is present in 70-85% of first strokes six months after stroke [49], which may greatly impact functional independence in simple activities of daily living post-stroke. In survivors randomized to one year of a standard diet (participants were given meals providing up to 125% of daily needs and high nutritional density) plus a) antioxidants alone (290 mg vitamin E, 240 mg vitamin C, 150 mg polyphenols and 19 mg β -carotene) b) omega 3s alone (500 mg polyunsaturated fatty acids) c) antioxidants plus omega 3s, or d) placebo [50], no effects were observed with regard to group differences in neurological or functional status [50] at one year; however, when omega-3 groups were combined, a trend in better improvements in functional status (i.e., Barthel Index (assesses autonomy in activities of daily living) and Rivermead Mobility Index (quantifies mobility disability)) and lower mortality were observed in those supplemented with omega 3s. This suggests that omega 3 supplementation may result in improved functional outcomes during the chronic phase of stroke.

Examination of vitamin D supplementation on fall risk also has occurred. Stroke survivors were supplemented with alphacalcidol 1 μ g daily for one year [51]. Alphacalcidol is active vitamin D₃ metabolite. Although a control group was not available, the authors did not find that vitamin D was associated with a decrease in fall prevention. However, among female stroke survivors in an institutional setting, a meta-analysis suggests a significant reduction in fall rate and proportion of fallers in those using vitamin D [52]. Further, supplementation with 1,000 IU vitamin D₂ daily for two years resulted in a 59% reduction in falls and improved muscle strength compared to a placebo in older, vitamin D deficient female stroke survivors with hemiplegia [53]. Thus, it appears that ensuring adequate vitamin D may have positive effects on physical functioning post-stroke.

Fracture risk

The incidence of hip fracture after a stroke is reported to be at least 1.5 times higher than in the general population [54,55]. However, few studies have examined nutritional intervention to improve bone mineral density (BMD) and/or reduce fracture risk in stroke survivors. There are several mechanisms by which B vitamins may influence bone health, including the actions of homocysteine on modulation of collagen cross-linking and formation, osteoclast formation, osteoblast formation, and bone turnover [56]. However, treatment with B vitamins does not appear to affect the overall incidence of skeletal fractures in the VITATOPS [57] or HOPE-2 [58] studies.

Because vitamin D helps the body absorb the minerals calcium and phosphorus its effects on bone health post-stroke also is examined. Sato et al. [59] examined the efficacy of 1 μ g 1-alpha-hydroxyvitamin D₃ and 300 mg supplemental elemental calcium daily for six months

on the maintenance of bone mass and hip fractures incidence after hemiplegic stroke (4.8 years stroke latency). BMD on the hemiplegic and intact side decreases to a lesser extent following supplementation with vitamin D than with the placebo (which also received the calcium supplement). The incidence of hip fracture also was less in the vitamin D supplemented group. However, baseline vitamin D concentrations were not reported and some studies in non-stroke populations suggest that vitamin D has the greatest effects in those that are vitamin D deficient. This is corroborated by another study by Sato et al. [53] in which a reduction in the incidence of hip fracture was observed following supplementation with 1,000 IU vitamin D₂ daily for two years in vitamin D deficient female stroke survivors with hemiplegia. Sunlight exposure also is shown to improve serum vitamin D concentrations and BMD in vitamin D deficient stroke survivors [60]. These data highlight the importance of optimizing vitamin D concentrations for maintenance of bone health post-stroke.

Subjective outcomes

Almost 30% of these survivors have depression that adversely affects their quality of life (QOL) [61]. Attempts to use antidepressants are largely unsuccessful in stroke survivors [62,63], and considering the adverse events associated with regular use of these medications [64], identifying non-therapeutic modalities to reduce depression is of great importance. In the VITATOPS study, treatment with B vitamins ranging from one to 10.5 years (mean 7.2 years) reduced the risk of a major depressive episode [32]. Conversely, the SU.FOL.OM3 trial found no effects of B vitamin supplementation on depressive symptoms in those with a cardiovascular disease history [65]. Interestingly, supplementation with omega 3s in men resulted in a 28% higher risk of presenting with depressive symptoms than those receiving a placebo, with no such increased risk observed in women.

In addition to depression, the SU.FOL.OM3 trial also examined QOL, finding that neither B vitamins nor omega 3s supplemented individually or in combination resulted in health related improvements in QOL [66]. The lack of an effect of fish oils on health related QOL or measures of anxiety, insomnia, and depression, were suggested by a previous study in stroke survivors (>3 months post stroke) that were supplemented for 12 weeks with 3 g of fish oil containing 700 mg DHA and 300 mg EPA [44]. However, supplementation with several micronutrients, including several B vitamins, in those with chronic heart failure, has resulted in improvements in QOL previously [67]. The current data provide insufficient evidence for the support of nutritional supplementation to reduce depression and improve QOL in chronic stroke.

Cognitive function

Approximately 16% of chronic stroke survivors are cognitively impaired [68], which is associated with worse recovery of activities of daily living post-stroke [69]. Trials that report a benefit of B vitamins on improving cognitive function in non-stroke participants typically do so in subjects with elevated homocysteine levels [70,71], which is observed in a third of stroke survivors [5]. The VITATOPS study found no effect on the incidence of cognitive impairment or cognitive decline, as measured by the Mini-Mental State Examination, during a median of 2.8 years of B vitamin supplementation [68]. Similar results were observed with the VISP study in that two years of high dose B vitamin supplementation did not influence plasma amyloid-beta protein concentrations, which are thought to be a hallmark of cognitive impairment and dementia [72]. However, the SU.FOL.OM3 trial [73]

found that subjects with ischemic stroke, supplemented with B vitamins combined with omega 3s, were >50% more likely to score better on temporal orientation tasks than those receiving a placebo. These data indicate that supplementation with omega 3s combined with B vitamins may be beneficial at preventing cognitive decline following stroke.

Outcome Measure	Trial	Population	Supplement	Duration of Follow-up	Results
Cardiovascular Risk	HOPE 2 trial [33]	Adults with known cardiovascular disease (9% with a history of stroke) (N=5,522)	Daily 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 vs. placebo	5 years	Supplementation reduced risk for overall stroke, but not stroke severity or disability
	VISP trial [34,35]	Stroke survivors (N=2,993)	Daily high dose (2.5 mg folic acid, 25 mg vitamin B6 and 400 µg vitamin B12) vs. low dose (20 µg folic acid, 0.2 mg vitamin B6 and 6 µg vitamin B12)	2 years (median)	High dose supplementation reduced recurrent vascular risk, but only in those >67 years old. High dose supplementation may increase the risk of recurrent stroke in those taking antiplatelet therapy.
	VITATOPS trial [37]	Stroke and transient ischemic attack survivors (N=285)	Daily 2 mg folic acid, 25 mg vitamin B6 and 0.5 mg vitamin B12 vs. placebo	6 months	Supplementation did not reduce blood concentrations of biomarkers of inflammation or hypercoagulability, but reduced homocysteine.
	VITATOPS trial [36,38,39]	Same as above (N=8,164)	Same as above	Up to 5 years (3.4 year median)	Supplementation reduced the risk for recurrent stroke, but only in those not taking antiplatelet drugs. Supplementation did not improve carotid intima-medial thickness or flow-mediated dilation or the progression of brain lesions.
	SU.FOL.OM3 trial [41]	Adults with known cardiovascular disease history (25% with a history of stroke) within the preceding 12 months (N=2,501)	Daily 1) 0.56 mg 5-methyltetrahydrofolate, 3 mg vitamin B6 and 0.02 mg vitamin B12, 2) 600 mg EPA and DHA in a 2:1 ratio, 3) B vitamins plus omega 3s or 4) placebo	4.7 years (median)	Supplementation with B vitamins reduced the risk of ischemic stroke (compared to placebo), but omega 3s had no significant effects on any major cardiovascular event
	Green et al. [43]	Stroke and transient ischemic attack survivors (N=11)	Daily EPA (180 mg) vs. olive oil control (cross over-design)	1.6 months	Supplementation had no effect on cholesterol fraction or platelet function.
	Poppitt et al. [44]	Stroke survivors >3 months post stroke (N=102)	Daily 300 mg EPA and 700 mg DHA vs. palm and soy oil control	3 months	Supplementation did not result in significant effects on serum lipids, inflammation or hemostatic markers.
	JELIS trial [45]	Hypercholesterolemic stroke survivors (N=18,645)	Daily statin+1800 mg EPA vs. statin alone	4.6 years (mean)	Supplementation resulted in a relative reduction in recurrent stroke risk.
	Witham et al. [48]	Stroke survivors with baseline 25(OH)D<75 nmol/L (N=58)	100,000 IU vitamin D2 vs. placebo	4 months	High dose oral vitamin D supplementation did not improve blood pressure or flow mediated dilatation.

Physical Function	Nutri-stroke trial [50]	Ischemic stroke survivors admitted to a rehabilitation unit (N=72)	Standard diet+daily 1) antioxidant (290 mg vitamin E, 240 mg vitamin C, 150 mg polyphenols and 19 mg β -carotene), 2) omega 3s (500 mg), 3) antioxidant+omega 3s 4) placebo	12 months	Omega-3 supplemented groups (combined) had a trend in better improvements in functional status and lower mortality.
	Sato et al. [53]	Older, vitamin D deficient female stroke survivors with hemiplegia (N=96)	Daily 1,000 IU vitamin D2 vs. placebo	2 years	Supplementation resulted in a reduction in fall incidence and improved muscle strength.
Fracture Risk	HOPE-2 trial [58]	Same as above (N=5,522)	Same as above	Same as above	Supplementation had no effect on osteoporotic fracture incidence.
	VITATOPS trial [57]	Same as above (N=8,164)	Same as above	3.4 years (median)	Supplementation had no effect on incidence of osteoporotic fractures.
	Sato et al. [59]	Stroke survivors with hemiplegia (N=64)	Daily 1.0 μ g 1-alpha-hydroxyvitamin D3+vs. placebo (all subjects also received 300 mg elemental calcium)	6 months	Supplementation prevented decreases in BMD on the hemiplegic side and reduced the incidence of hip fractures.
	Sato et al. [53]	Same as above (N=96)	Same as above	Same as above	Supplementation reduced the incidence of hip fracture.
Subjective outcomes	VITATOPS trial [32]	Same as above (N=273)	Same as above	7.2 years (mean)	Supplementation reduced the risk of a major depressive episode.
	SU.FOL.OM3 trial [65,66]	Same as above (N=2,000)	Same as above	Same as above	Supplementation of B vitamins had no effects on depressive symptoms or health related QOL. However, supplementation with omega 3s in men resulted in a higher risk of presenting with depressive symptoms (compared to placebo).
	Poppitt et al. [44]	Same as above (N=102)	Same as above	Same as above	Supplementation had no effect on health related QOL or measures of anxiety, insomnia and depression.
Cognitive Function	VITATOPS trial [68]	Same as above (N=8,164)	Same as above	2.8 years (median)	Supplementation had no effect on the incidence of cognitive impairment or cognitive decline.
	VISP trial [72]	Same as above (N=300)	Same as above	Same as above	Supplementation did not influence plasma amyloid-beta protein concentrations, (marker of cognitive impairment and dementia).
	SU.FOL.OM3 trial [73]	Same as above (N=2,000)	Same as above	Same as above	Supplementation with B vitamins combined

					with omega 3s resulted in better scores on temporal orientation tasks (compared to placebo).
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Table 1: Evidence for the use of nutritional supplementation in chronic stroke survivors from clinical trials.

Conclusion

There is growing evidence for the role of nutrition in the development of new strategies for stroke rehabilitation. It appears that a combination of screening methods, including food record, laboratory, and malnutrition screening tools assessments may be beneficial to assess the dietary intake adequacy of chronic stroke survivors. Behavior modification and encouragement of oral intake through retraining of eating abilities and alteration of dining condition shows promise in the promotion of optimal nutrient intake. Some, but not all studies support the use of B vitamins on secondary stroke prevention and reductions in fracture and depressive symptom risk, especially in older chronic stroke survivors with elevated homocysteine concentrations. Results of vitamin D supplementation studies appear encouraging to improve physical function and reduce fracture risk in stroke survivors with vitamin D deficiency. Further, omega 3s may have promising effects on function when supplemented alone and on cognitive function when supplemented with B vitamins. However, to date, study limitations, such as differences in subject characteristics (i.e., various ages and stages of disease/neurologic impairment), make drawing conclusions regarding the impact of nutritional supplementation difficult. Further research is needed to provide insight on the ideal supplement dose and duration and about how different rehabilitation therapies (i.e., nutritional supplements, medications, exercise, and caloric restriction) may interact to affect recovery. This information may one day help to individualize rehabilitation approaches to optimize patient outcomes during the chronic phase of stroke (Table 1).

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