Lipids in Health and Disease

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Efficacy of an avocado-based Mediterranean diet on serum lipids for secondary prevention after ischemic stroke: a randomized phase 2 controlled pilot trial

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Abstract

Background The impact of a healthy diet on the secondary prevention of ischemic stroke (IS) remains uncertain. Levels of low-density lipoprotein cholesterol (LDL-C) are inversely associated with the risk of IS recurrence. A Mediterranean diet (MeDi), consisting of a preference for fish/poultry, monosaturated fats from olive oil, fruit, vegetables, whole grains, legumes/nuts and limited red meats, animal fats and sweetened beverages, reduces metabolic syndrome, LDL-C levels and stroke risk. Avocados also reduce metabolic syndrome and LDL-C levels but are not part of the traditional MeDi diet. The effects of an avocado-based Mediterranean diet on LDL-C were investigated and compared to those of a low-fat diet in patients with previous IS.

Methods The Avocado-Based Mediterranean Diet on Serum Lipids for Secondary Prevention after Ischemic Stroke (ADD-SPISE) was a prospective, randomized, open-label, blinded outcome assessment, phase 2, clinical trial. The participants were adults with an IS in the previous month who were randomly assigned at a 1:1 ratio to a MeDi or a low-fat diet for three months. Outcome assessors of laboratory results and data analysts were masked. The primary outcome was the mean difference in LDL-C between groups at 90 days, adjusted by statin use. Safety, feasibility and acceptability (assessed through a 14-item questionnaire administered to all patients who completed the follow-up) were also evaluated.

Results From August 2018 to October 2022, 200 participants were enrolled (97 randomized to the low-fat diet and 103 to the MeDi), with 189 (94.5%) completing the study. There were no significant differences in LDL-C levels between the MeDi group and the low-fat group at 90 days: 66.5 mg/dL (95% confidence interval [CI] 59.6, 73.4) in the MeDi group and 69.9 mg/dL (62.6, 77.2) in the low-fat group at the end of follow-up. The adjusted difference was −3.4 mg/dL (-13.4, -6.62); $P=0.50$. The intervention group showed significant improvements in Mediterranean diet adherence ($P<0.01$). Moreover, no significant differences in adverse events were observed between the groups.

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Conclusion Compared with a low-fat diet, the avocado-based MeDi did not significantly lower LDL-C in IS patients after three months. The intervention was safe, feasible, and well accepted. Larger trials should establish whether longer dietary interventions could yield clinically significant benefits in these patients. The study is registered under ADD-SPISE at www.clinicaltrials.gov. Identifier: NCT03524742.

Keywords Ischemic stroke, Secondary prevention, Mediterranean diet, Avocado, LDL cholesterol

Introduction

A global burden of disease study revealed that dietary risk contributed to 31% of stroke-related disability-adjusted life years [1]. Similarly, the INTERSTROKE study reported that an unhealthy diet was responsible for 21% of the population's attributable risk of ischemic stroke (IS) [2].

There is consistent evidence that a Mediterranean diet (MeDi) is associated with a lower risk of cardiovascular disease (CVD), including IS [3, 4]; this finding is supported by a recent systematic review and meta-analysis of observational studies that revealed an 18% reduction in the risk of IS with MeDi [5]. However, a Cochrane review of MeDi for the primary and secondary prevention of CVD reported that the evidence of a reduction in the risk of IS in primary prevention was of moderate quality [6]. Current secondary prevention guidelines recommend a MeDi after IS but on the basis of extrapolations from observational and primary prevention trials and not secondary prevention trials [7, 8]. MeDi, which is based on extra virgin olive oil and whole nuts as a source of monounsaturated fatty acids (MUFAs), reduces metabolic syndrome, systolic and diastolic blood pressure, LDL-C, body mass index (BMI) and waist circumference (WC) and can also affect inflammation. Furthermore, several beneficial nutrients abundant in MeDi could act on inflammatory biomarkers, such as adhesion molecules, cytokines, or molecules related to the stability of atherosclerotic plaques, such as apolipoproteins [9, 10]. Avocados are a frequently used nutrient-dense source of MUFAs rich in vitamins, minerals, fiber, phytosterols, and polyphenols that can also reduce LDL-C and metabolic syndrome, but they have not been purposefully added to MeDi in most trials [11–13] and the consumption of avocado as part of traditional MeDI has increased [14]. A systematic review and meta-analysis of 7 randomized trials reported that compared with low-fat or habitual diets, avocado-rich diets were associated with decreased LDL-C levels [12]. This is important because LDL-C levels are inversely associated with the risk of IS recurrence, and interventions that reduce their levels are both efficacious and safe in decreasing this risk [15]. The ADD-SPISE trial aimed to investigate the efficacy of a MeDi based on avocados compared with a low-fat diet in reducing LDL-C and other cardiometabolic and inflammatory risk factors in patients with a recent IS as well as the safety, feasibility and acceptability of the intervention. The ADD-SPISE trial is the second and largest study on secondary stroke prevention investigating the effects of a Mediterranean diet in patients with a history of stroke. It is also the only trial examining the impact of an avocado-based Mediterranean diet, specifically in this high-risk group.

Methods

Study design

The ADD-SPISE trial was an investigator-led, open-label, prospective, phase 2b, single-center, controlled superiority study using a 'proof-of-concept' approach with blinded outcome assessments (PROBE design). The full details of the trial design have been previously published [16]. During the first year of the trial, the protocol was revised to eliminate the upper age limit of 85 years and to extend eligibility criteria for tobacco use to include participants who were active smokers or had quit within the past two years. Owing to the pandemic, further amendments were made to extend the follow-up period from 15 to 30 days, enable home sampling, allow for online consent signatures, and introduce a trial acceptability questionnaire after the randomization of 20 patients (Table S1). Ethics approval for the initial protocol and its revisions was granted by the Universidad del Desarrollo, Clínica Alemana de Santiago Scientific Ethics Committee (ID 2018–43). Data will be made available upon reasonable request to the corresponding author.

Eligibility

The study enrolled adults aged 45 years or older who had been admitted to Clínica Alemana de Santiago due to an ischemic stroke (either imaging-confirmed cerebral infarction or transient ischemic attack) within the previous month before randomization. Eligible participants also had at least one cardiovascular risk factor, including hypertension, type 2 diabetes, insulin resistance, dyslipidemia (high LDL-C or total cholesterol), current smoking, coronary heart disease, a BMI of 25 or higher, or a family history of premature cardiovascular disease. Exclusion criteria included comorbidities that would hinder adherence to the interventions or make dietary changes unlikely, known allergies or intolerances to avocados, feeding limitations such as dysphagia, required use of medications that might alter lipid levels, or a life expectancy of less than three months owing to another illness that could affect outcome assessments or follow-up.

Patients whose ischemic stroke was linked to causes such as arterial dissection, thrombophilia, reversible cerebral vasoconstriction syndrome, vasculitis, or autoimmune-related stroke were also excluded [16]. All patients provided written informed consent to participate in the trial.

Randomization and blinding

After providing consent, patients were randomized to one of two dietary intervention groups at a 1:1 ratio via a minimization algorithm. The assignment was stratified on the basis of sex, age (< 70 or ≥ 70 years), and prior adherence to the Mediterranean diet, as determined by the Mediterranean Diet Adherence Screener (MEDAS) score (< 7 or ≥ 7) [15]. A study investigator communicated the assigned diet to the study dietitian, and the principal investigator ensured that each participant received the correct dietary intervention.

While neither the participants nor the investigators were blinded to the assigned diets, laboratory outcome assessors, including those measuring LDL-C and other laboratory results, as well as data analysts, were unaware of the diet assignments.

Procedures

The intervention period lasted up to 90 (± 30 as a buffer for varying patient needs) days and included two dietary approaches: (A) A Mediterranean diet rich in avocados, where at least 35% of total calories came from fat (22% from monounsaturated fats (MUFAs), 6% from polyunsaturated fats (PUFAs), and less than 10% from saturated fats), along with 15% of calories from protein and a maximum of 50% from carbohydrates. (B) A low-fat, high-complexity carbohydrate diet recommended by the National Cholesterol Education Program and the American Heart Association, with less than 30% total calories from fat (less than 10% from saturated fat, 12–14% from MUFAs, and 6–8% from PUFAs), 15% protein, and at least 55% carbohydrates [17]. Both diets included complex carbohydrates such as whole grains, fruits, vegetables, and legumes, along with low-fat meat and dairy, with minimal or no simple sugars. In the avocado-based Mediterranean diet, participants were advised to eat half an avocado daily (approximately 90 g, providing approximately 8 g of MUFAs), use olive oil as the primary fat source, and consume nuts daily. In contrast, the low-fat diet restricted foods rich in avocado and MUFAs [11]. Both diets were adjusted to be normocaloric according to each patient's nutritional needs and activity level (Table 1). At the baseline visit, patients received in-person nutritional counseling and education on their assigned diet; during the pandemic, online virtual sessions were included when deemed necessary. Follow-up phone calls were made at 30 and 60 days by the same dietician, who reviewed the patient's adherence to the dietary plan and provided personalized feedback, recommendations, and reinforcements for the assigned intervention. Additionally, patients were given comprehensive written materials, including lists of typical foods for their diet, seasonal shopping guides, meal plans, and 14-day recipe collections. Over the course of the 3-month intervention, each patient had at least three sessions with the study dietician. Dietary adherence was evaluated via food frequency questionnaires, 24-hour dietary recall, and the Mediterranean Diet Adherence Screener (MEDAS). The MEDAS is a 14-item questionnaire that assesses food intake patterns, with each item scored as either 1 point or 0 points, on the basis of whether the participant meets the criteria for adherence to each specific component of the Mediterranean diet [16]. The food surveys were analyzed both qualitatively and quantitatively. The qualitative analysis focused on factors such as the number of daily meals, fluid intake, and overall quality of the food consumed and compared these factors between the diet groups. For the quantitative analysis, data were collected on the ingredients and quantities of foods consumed the day before each visit. The percentage of adequacy was calculated via the formula ([intake value/requirement value]*100), with nutrient intake deemed adequate if it fell between 90% and 110%.

To ensure adherence to the dietary protocol, the study nutritionist consistently reinforced the importance of following the assigned portions and meal frequencies during each interaction and addressed any patient-specific concerns. All participants also received standard care for secondary stroke prevention, which included antithrombotics, high-dose statins (typically atorvastatin 80 mg/day), antihypertensives, and hypoglycemic agents if needed. During each visit, patients were reminded to continue their prescribed medications for secondary prevention.

Outcomes

The primary efficacy outcome was a significantly lower mean plasma LDL-C level at 3 months in the intervention diet group than in the control group. The predefined secondary outcomes included the following: (1) improvements in the serum lipid profile (mean total cholesterol, mean HDL-C, mean non-HDL-C, mean total cholesterol/HDL-C ratio and mean triglycerides), mean fasting plasma glucose, mean insulin levels and mean homeostatic model (HOMA) index; (2) reductions in the mean serum inflammation marker levels (apolipoprotein A1, apolipoprotein B, interleukin 6, and intercellular adhesion molecules [ICAM-1], and vascular cell adhesion molecules [VCAM-1]; 3) improvements in the anthropometric measurements (mean body mass index, mean waist circumference, mean waist–hip ratio and mean waist–height; 4) safety assessments (adverse and serious

Table 1 Summary of dietary recommendations for the patients in each intervention group of the **ADD-SPISE** study

Item	Mediterranean diet	Low fat diet
Oil used for cooking and salads	Extra virgin olive oil only. Four or more teaspoons per day (> 20 cc/day)	Canola oil for cooking and olive oil 2 teaspoons per day (10 cc/day)
Fruits	Three portions per day	Three portions per day
Vegetables/salads	The portion of fresh vegetables or salads must be at least 1 cup (200 gr), both at lunch and dinner	Same recommendation as in the Mediterranean Diet group
Grains	Every day at breakfast, lunch, and teatime. Preferably whole grains (bread, oatmeal, rice, pasta)	Same recommendation as in the Mediterranean Diet group, but the size of the portion was bigger (to reach the 55% of carbohydrate intake)
Legumes	Three times per week	Three times per week
Dairy products	Two servings per day of low-fat dairy products	Same recommendation as in the Mediterranean Diet group
Tree nuts	One serving per day (30 gr)	Occasional consumption: one serving or less per week.
Avocado	At least ½ avocado (90 gr) per day for 3 months	Less than 3 times a week (1/4 unit every time)
Fish	Three times per week	Three times per week
White meat	Chicken, turkey instead of red meat at least three times per week	Same recommendation as in the Mediterranean Diet group
Red meat or processed meats	Once a week	Once a week
Eggs	Twice a week	Three times a week
Butter and margarine	Not recommended	One serving or fewer per week allowed
Wine	Optional consumption. In case of a habitual wine drinker one glass per day for women and two glasses per day for men.	Optional consumption. In case of a habitual wine drinker one glass per day for women and two glasses per day for men.
Culinary techniques	Use of sofrito (garlic, onion, and natural tomato sauce slowly cooked in olive oil) at least twice a week	Not recommended
Commercial bakery products, sweets, and pastries	Not recommended	Not recommended
Sweet or carbonated beverages	Not recommended	Not recommended

For each intervention, three different daily caloric dietary contributions were made: 1500, 1800, and 2000 calories and a maximum of 5 g of salt per day

adverse events); and 5) assessments of feasibility, adherence, and acceptability.

Statistical analysis

The sample size was calculated assuming a difference of 4.6 mg/dL (SD 1.4) or more between groups at 90 days. This difference was estimated on the basis of the results of 3 studies published before the ADD-SPISE was planned, investigating the effect of an avocado-based diet on LDL-C [18–20]. A total sample size of 200 patients (100 per group) was calculated to provide 80% statistical power at the 5% significance level, accounting for a 10% dropout rate and 5% crossover. Efficacy analyses were conducted on the intention-to-treat (ITT) population, defined as those initiating the allocated diet. The primary outcome (mean LDL-C) between the two groups was compared at the end of follow-up, with adjustments for statin dose, and least square means were calculated along with 95% confidence intervals. Similar analyses were performed for all secondary outcomes (mean levels of serum lipids, fasting plasma glucose, insulin levels, HOMA, serum inflammation markers, and anthropometric measurements), adjusting for confounding factors such as previous metabolic syndrome, sedentary lifestyle, and oral hypoglycemic use (specifically for glucose, insulin, and HOMA levels). Multiple imputations using chained equations were applied to address missing data, assuming randomness. Sensitivity analysis was conducted on patients with complete datasets. Safety analyses included all study participants, with records kept for adverse events (AEs), serious adverse events (SAEs), and any discontinuations due to SAEs. Binary outcomes, including SAEs, major cardiovascular events, and death, were analyzed via Fisher's exact test. Feasibility, defined by the average time from symptom onset to intervention, was assessed via Student's t test, whereas the proportion of patients who completed the intervention at 3 months was compared via Fisher's exact test. Adherence was assessed in two distinct ways only for patients who completed the study: (a) by comparing MEDAS scores through the Wilcoxon rank-sum (Mann–Whitney) test as an ordinal scale and (b) by calculating the percentage of dietary adequacy ([intake value/requirement value]*100) at 1, 2, and 3 months, which was analyzed via generalized

linear mixed models for repeated measures both within and between groups. Trial acceptability was measured through a 14-item questionnaire administered to all patients who completed the follow-up and was analyzed via the Mann–Whitney–Wilcoxon test. Prespecified subgroup analyses for the primary outcome were conducted by including an interaction term in the models and adjusting for baseline LDL-C and statin use. Subgroups were defined on the basis of age (< or ≥ 69 years), sex, education level (< or ≥ 12 years), poststroke disability (modified Rankin score < or ≥ 1), physical activity (RAPA score < or ≥ 6), MEDAS score (< or ≥ 6), presence of dyslipidemia, diabetes or insulin resistance, BMI (< or ≥ 25), and BMI (< or ≥ 30) [21]. A prespecified per-protocol analysis of the primary outcome was also conducted for patients who adhered to the assigned diet for at least 6 weeks, including one patient who crossed from a low-fat diet to a Mediterranean diet. A post hoc analysis was carried out to calculate the least square means of the differences in LDL-C from baseline values with corresponding 95% confidence intervals adjusted for statin use. The significance level for alpha was set at 0.05, and all the data were analyzed via STATA (version 16.0, StataCorp). Owing to the low risk of the intervention and the absence of interim analysis, a data monitoring committee was not needed. All adverse events were adjudicated by a clinical events committee.

Results

From August 15, 2018, to October 10, 2022, 911 patients were screened for eligibility, and 200 (21.9%) were included in the ADD-SPISE trial. A total of 103 (51.5%) were randomized to the avocado-based MeDi diet, and 97 (48.5%) were randomized to the low-fat diet. The baseline demographic and clinical characteristics were well balanced in both groups in terms of age and sex and other important variables except for HDL-C, which was lower in the MeDi group (Table 2). The population sample was predominantly male (63.5%), and the mean age was 69.2 (10.4) years. At the end of follow-up, on January 19, 2023, 15 patients had abandoned the dietary intervention: 6 (5.8%) in the MeDi group and 9 (9.2%) in the low-fat diet group ($P = 0.35$). The reasons for dropout were similar in both groups, as described in Fig. 1. Ninety-four-day LDL-C levels were missing for 3 patients in the MeDi diet group and 4 patients in the low-fat diet group and were imputed. The mean time from symptom onset to diet intervention was 12.8 (7.4) days, without a difference between the groups ($P = 0.54$). Baseline adherence to the MeDi was 6 (interquartile range [IQR] 5–8) on the 0–14 MEDAS scale and was not different between groups ($P = 0.7$). At 3 months, this score had increased to 10 (IQR 8–11) in the MeDi group and to 8 (IQR 7–10) in the low-fat diet group ($P < 0.01$). This increase was significant for the most specific MeDi components associated with olive oil use, nuts, and avocado consumption in the MeDi group (Table 3). There were no significant changes in total caloric, lipid, carbohydrate, or protein intake with diet intervention. Patients in the MeDi group had greater overall adequacy of the diet intervention regarding the consumption of fat, carbohydrates, and calories (Tables S2 and S3). The acceptability of the trial was high and equivalent for both diet interventions ($P = 0.16$) (Table S4). At 90 days, the mean LDL-C was 66.5 mg/dL (59.6, 73.4) in the MeDi group and 69.9 mg/dL (62.6, 77.2) in the low-fat group. The difference was −3.4 mg/dL (-13.4, 6.62); $P = 0.50$ (Table 4). In patients who adhered to the trial protocol and were allocated to the diet (per protocol population), the mean LDL-C was 67.2 mg/dL (60.3, 74.2) in the MeDi group and 70.1 mg/dL (62.6, 77.5) in the low-fat group. The difference was −2.83 mg/dL (-13.1, 7.38); $P = 0.58$. The secondary outcomes are also described in Table 3. There were no significant differences in any of the lipid profile components between the groups. Similarly, we did not find any significant differences in glycemia control, anthropometric measures or inflammatory markers between the groups.

There were comparable numbers of serious adverse events between the groups, with no differences in stroke recurrence or cardiovascular events or in the number of nonserious adverse events (Table 5 and Table S5).

There was no evidence of heterogeneity in the effects of the treatment for any of the prespecified subgroups (Fig. 2). Sensitivity analysis revealed no differences in the primary endpoint between groups (Table 4). The results of the post hoc analysis were not different from the primary results and are shown in Table S6.

Discussion

In our study comparing a 3-month avocado-modified Mediterranean diet with a low-fat diet in 200 recent ischemic stroke patients, we found no significant difference in mean LDL-C levels between the two diets at the end of follow-up, although both diets reduced LDL-C levels from baseline (Table S6). This result is comparable to the findings described by Estruch et al. in a short primary prevention trial, who reported nonsignificant reductions of 3.9 and 3.4 mg/dL in LDL-C in patients receiving a MeDi diet compared with those receiving a low-fat diet [22]. Previous secondary prevention trials with MeDi reported no differences in LDL-C levels after longer follow-up but did not include stroke patients or adjust for statin use [23, 24]. A Cochrane review revealed very low-quality evidence that MeDi had little or no effect on LDL-C levels in secondary prevention compared with other diets, with a small number of trials and patients included [6]. Although only exploratory, we found no significant differences between interventions in any

Table 2 Baseline characteristics

	Mediterranean diet group (*n* = 103)	Low-fat diet group (*n* = 97)	*P* value
Age, years	68.5 (10.9)	69.8 (9.8)	0.41
Sex			0.77
Female	33 (34.9)	37 (38.1)	
Male	67 (65.1)	60 (61.9)	
Education, ≥ 12 years	83 (82.2)	82 (84.5)	0.75
Ethnicity			0.11
Hispanic/mestizo	90 (87.4)	75 (77.3)	
White	13 (12.6)	21 (21.6)	
Asian	0 (0)	1 (1.03)	
Hypertension*	65 (63.1)	58 (59.8)	0.55
Diabetes*	18 (17.5)	16 (16.5)	0.90
Insulin resistance*	20 (19.4)	13 (13.4)	0.27
Dyslipidemia*	73 (70.9)	63 (65.0)	0.32
Current smoking	18 (17.5)	15 (15.5)	0.74
Alcohol abuse	2 (1.9)	2 (2.1)	0.93
History of previous stroke or transient ischemic attack	19 (18.4)	13 (13.4)	0.36
History of any cardiopathy	30 (29.1)	34 (35.0)	0.48
Atrial fibrillation	10 (9.7)	17 (17.5)	0.45
History of renal failure	3 (2.9)	3 (3.1)	0.92
History of sleep apnea	6 (5.8)	9 (9.3)	0.33
History of mood disorder	13 (12.6)	11 (11.3)	0.82
History of previous malignancy	7 (7.8)	5 (5.2)	0.47
Metabolic syndrome†	57 (58.8)	57 (55.3)	0.62
Sedentary lifestyle‡	90 (88.2)	79 (84.9)	0.33
Baseline modified Rankin score	0 (0–2)	0 (0–2)	0.56
Baseline diet			
Mediterranean diet adherence screener score (MEDAS)	6 (5–8)	6 (5–8)	0.89
Avocado consumption, ≥ 3.5 per week	27 (26.2)	21 (21.7)	0.41
Baseline medication			
Lipid lowering drugs including statins	103 (100)	97 (100)	1.0
Blood pressure lowering drugs	84 (81.6)	72 (74.2)	0.18
Antiplatelets	83 (80.6)	72 (74.2)	0.24
Anticoagulants	13 (12.6)	20 (20.6)	0.11
Hypoglycemics	34 (33.4)	22 (22.7)	0.12
Qualifying event			0.32
Ischemic stroke	83 (80.6)	73 (75.3)	
Transient ischemic attack	20 (19.49	24 (24.7)	
NIHSS§	1 (0–4	1 (0–4)	0.51
ABCD2 score¶	3.5 (2–4)	4 (3–5)	0.14
TOAST‖			
Cardioembolic	24 (23.3)	27 (27.8)	0.62
Large vessel disease	24 (23.3)	17 (17.5)	0.34
Small vessel disease	10 (9.7)	17 (17.5)	0.09
Cryptogenic	40 (38.8)	31 (32.0)	0.36
Other/undetermined cause	1 (1.0)	3 (3.1)	0.27
Reperfusion therapies			
Thrombolysis	31 (30.1)	26 (26.8)	0.45
Thrombectomy	9 (8.7)	11 (11.3)	0.50
Clinical and laboratory variables			
Systolic blood pressure, mm Hg	130.0 (16.8)	130.3 (20.0)	0.69
Diastolic blood pressure, mm Hg	76.8 (12.7)	75.8 (12.1)	0.60
Weight, kg	77.2 (14.6)	77.0 (13.2)	0.46

Table 2 (continued)

	Mediterranean diet group (*n* = 103)	Low-fat diet group (*n* = 97)	*P* value
Body-mass index, kg/m^2	27.2 (4.1)	26.7 (6.2)	0.41
Waist circumference, cm	95.1 (12.4)	96.6 (13.3)	0.48
Waist-hip ratio, cm	0.95 (0.08)	0.96 (0.09)	0.40
Height to waist ratio	1.79 (0.21)	1.76 (0.24)	0.29
Total cholesterol, mg/dL	133.5 (37.1)	136.7 (33.7)	0.77
LDL cholesterol, mg/dL	75.0 (33.1)	74.8 (29.3)	0.79
HDL cholesterol, mg/dL	43.7 (12.4)	47.5 (12.6)	0.03
Non-HDL cholesterol, mg/dL	89.8 (34.7)	89.2 (30.5)	0.89
Total cholesterol/HDL cholesterol ratio	3.2 (1.1)	3.0 (0.9)	
Triglycerides, mg/dL	111.7 (50.6)	106.8 (46.9)	0.08
Fasting plasma glucose, mg/dL	104.5 (21.5)	102.9 (18.4)	0.61
Insulin, mg/dL	12.9 (6.6)	12.5 (7.3)	0.61
HOMA index**	3.4 (2.0)	3.2 (2.1)	0.60
Apolipoprotein A1, mg/dL	114.3 (34.9)	127.0 (50.6)	0.06
Apolipoprotein B, mg/dL	75.7 (23.3)	72.3 (23.9)	0.40
Interleukin 6, pg/mL	9.8 (24.2)	5.6 (5.6)	0.28
ICAM-1, ng/mL††	256.0 (197.8)	236.5 (154.1)	0.56
VCAM-1, ng/mL‡‡	844.1 (349.9)	793.1 (281.1)	0.31
Oleic acid, umol/mL	404.1 (243.8)	403.5 (275.1)	0.55

Data are presented as the mean (SE), median (IQR) or n (%). *Defined as documented previous clinical history of or on treatment for. †As defined in the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) report; waist circumference of more than 102 cm (40 in) in men and more than 88 cm (35 in) in women; triglyceride levels of at least 150 mg per dL (1.70 mmol per L); high-density lipoprotein cholesterol levels of less than 40 mg per dL (1.04 mmol per L) in men and less than 50 mg per dL (1.30 mmol per L) in women; blood pressure of at least 130/85 mm Hg; and fasting glucose levels of at least 110 mg per dL (6.10 mmol per L). ‡ Defined as Rapid Assessment of Physical Activity (RAPA-1) of 5 or less §National Institutes of Health Stroke Scale. Age, Blood pressure, Clinical features, Duration, Diabetes.||Trial of Org 10,172 in Acute Stroke Registry. **Homeostasis model assessment (a measure of insulin resistance). ††Intercellular adhesion molecules. ‡‡ Vascular cell adhesion molecules

secondary endpoint. Our data, though underpowered due to the small sample size, do not confirm previous findings that avocado diets significantly lower TC and triglycerides or that they increase HDL cholesterol [11–13]. The absence of significant differences in inflammatory markers or anthropometric measures between diets, as reported in previous studies, may also be due to the study's limited power [25].

The addition of an avocado to the MeDi diet did not result in any specific significant effect above that expected from a MeDi diet. We implemented this modification aimed at accommodating the European-style MeDi to align more closely with Latin American dietary preferences. This adaptation is especially pertinent due to the prominent dietary role that avocados play in the daily dietary practices of Chile, as opposed to the lower consumption of olive oil, which can be attributed to prevailing cultural traditions as well as cost [26]. These results are similar to those reported in the HAT study, which randomized individuals with an elevated waist circumference to a diet with 1 large avocado per day for 6 months rather than a habitual diet to decrease visceral adiposity and reported no significant group differences in components of the metabolic syndrome or lipid profile, including LDL-C, body weight, body mass index, and insulin levels [25]. In contrast, a recent small randomized clinical trial investigating the effects of daily avocado consumption in overweight or obese individuals tested three different cholesterol-lowering diets: a lower-fat diet (LF), a moderate-fat diet (MF) using high-oleic acid oils, and an avocado-based moderate-fat diet (AV) with one Hass avocado per day. Compared with the other diets, the AV diet resulted in a significantly greater reduction in LDL-C and non-HDL cholesterol. It also lowered LDL particle numbers, small dense LDL cholesterol, and the LDL/HDL ratio more effectively [27].

Our results indicate that the intervention was safe, feasible, and acceptable. The 4-point increase in MEDAS adherence in the MeDi group was significantly greater than that in the control group. This finding is relevant, as being in the high-adherence tertile has been reported to improve cardiovascular risk factors. Additionally, a 2-point increase in the MEDAS score is associated with a 10% lower stroke risk [28].

Strengths and limitations

Our study has several strengths. The high retention rate and significant changes in dietary habits in the MeDi group compared with those in the control diet group indicate its internal validity. Similarly, the low frequency of adverse events and high acceptability demonstrate

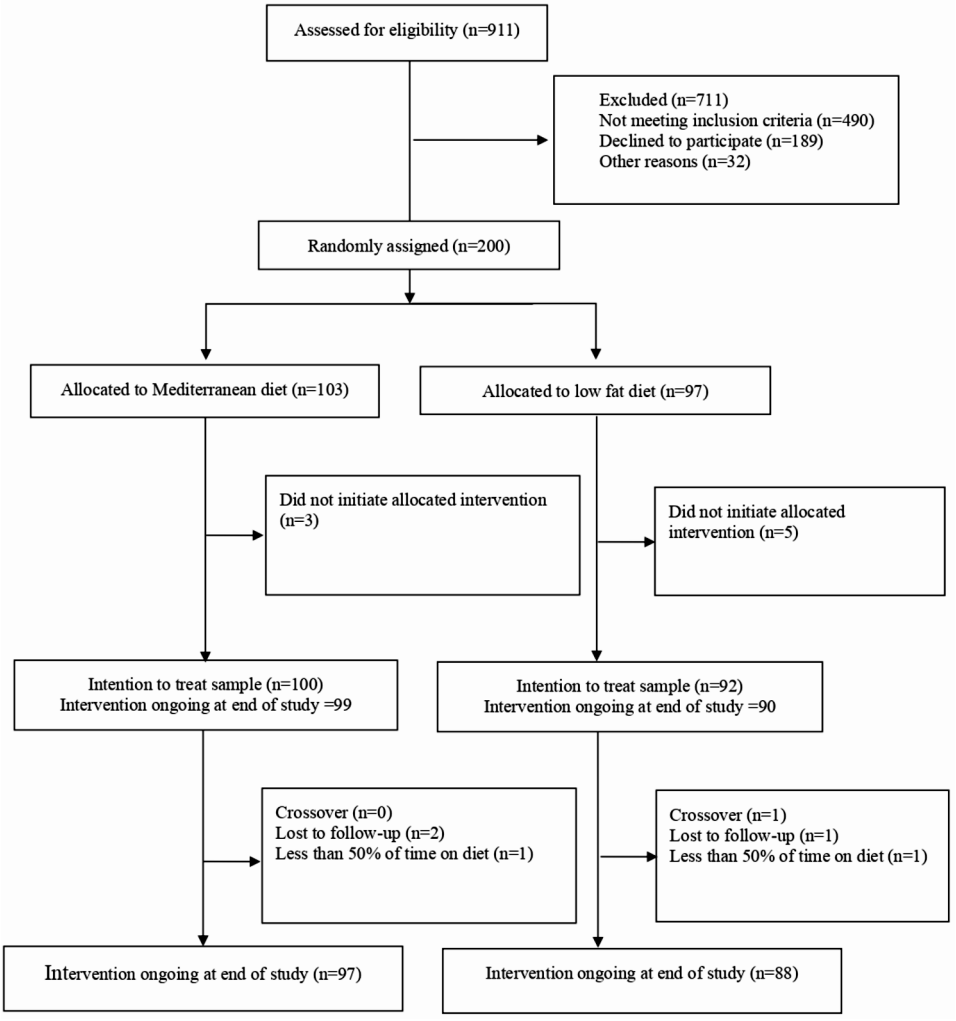

Fig. 1 Trial profile

Table 3 Changes in the consumption of key food items of the 14-Point Mediterranean Diet Adherence Screener (MEDAS)

Item	Baseline		*P*	3 months		*P*
	MeDi* *N* = 101	Low fat diet *N* = 91		MeDi* *N* = 97	Low fat diet *N* = 83	
1. Olive oil use.	65 (64.4)	59 (64.8)	1.00	96 (92.9)	55 (62.5)	< 0.001
2. Olive oil servings.	26 (25.7)	25 (27.5)	0.87	47 (46.5)	23 (26.1)	0.004
3. Vegetables servings.	57 (56.4)	58 (63.7)	0.37	78 (77.2)	64 (72.3)	0.50
4. Fruit servings	33 (32.7)	28 (30.8)	0.87	44 (43.6)	45 (51.1)	0.31
5. Red meat, hamburger, or meat products (ham, sausage, etc.) servings.	76 (75.2)	72 (79.1)	0.60	97 (96.0)	82 (93.2)	0.51
6. Butter, margarine, or cream servings.	50 (49.5)	48 (52.7)	0.66	94 (93.1)	85 (96.6)	0.34
7. Sweetened beverages consumption.	58 (57.4)	56 (61.5)	0.65	90 (89.1)	84 (95.4)	0.17
8. Wine consumption.	27 (26.7)	30 (32.9)	0.42	24 (23.8)	22 (25.0)	0.86
9. Legumes servings.	29 (28.7)	20 (21.9)	0.32	23 (22.8)	17 (19.3)	0.59
10. Fish or shellfish/seafood servings.	20 (19.8)	15 (16.5)	0.58	29 (28.7)	26 (29.6)	1.00
11. Commercial sweets or pastries consumption.	53 (52.5)	39 (42.9)	0.19	90 (89.1)	82 (93.2)	0.44
12. Nuts consumption.	40 (39.6)	32 (35.2)	0.55	80 (79.2)	35 (39.8)	< 0.001
13. Chicken, turkey, or rabbit meat preference.	63 (42.4)	67 (73.6)	0.12	98 (97.0)	83 (94.3)	0.47
14. Sofrito use.	39 (38.6)	39 (42.7)	0.56	76 (75.2)	47 (53.4)	0.002
Avocado consumption	26 (25.7)	21 (23.1)	0.73	95 (94.1)	17 (18.7)	< 0.001

*MeDi: Mediterranean Diet

Table 4 Primary and secondary outcomes of the Mediterranean diet and low-fat diet groups

Endpoint variable	Mediterranean diet group (*n* = 100)	Low-fat diet group (*n* = 92)	Difference	*P* value
Primary outcome ITT population†				
LDL cholesterol, mg/dL*	66.5 (59.6, 73.4)	69.9 (62.6, 77.2)	-3.4 (-13.4, 6.62)	0.50
Secondary outcomes ITT population				
Total cholesterol, mg/dL	129.8 (121.9, 137.7)	132.2 (123.9, 140.5)	-2.41 (-13.9, 9.1)	0.67
HDL cholesterol, mg/dL	50.3 (47.9, 52.8)	50.8 (48.2, 53.4)	-0.43 (-4.04, 3.17)	0.81
Total cholesterol/HDL cholesterol	2.70 (2.49, 2.91)	2.73 (2.50, 2.96)	-0.02 (-0.34, 0.29)	0.87
Non-HDL cholesterol	79.4 (71.7, 87.2)	81.4 (73.2, 89.6)	-1.97 (-13.2, 9.29)	0.73
Triglycerides, mg/dL	110. 3 (99.7, 120.9)	98.1 (86.9, 109.3)	12.1 (-3.29, 27.6)	0.12
Fasting plasma glucose, mg/dL	106.5 (103.0, 110.1)	102.2 (98.5, 105.8)	4.4 (-0.73, 9.49)	0.09
Insulin, mg/dL	12.7 (11.5, 13.9)	11.2 (9.90, 12.5)	1.53 (-0.25, 3.32)	0.09
HOMA‡	3.40 (3.03, 3.77)	2.87 (2.48, 3.25)	0.53 (-0.01, 1.07)	0.05
Apolipoprotein-A, mg/dL	138.6 (128.9, 148.5)	141.4 (131. 1, 151.7)	-2.74 (-17.0, 11.5)	0.70
Apolipoprotein-B, mg/dL	71.8 (67.5, 76.1)	65.9 (61.4, 70.5)	5.83 (-0.42, 12.1)	0.07
Interleukin-6, pg/mL	3.34 (2.72, 3.96)	3.52 (2.86, 4.179	-0.17 (-1.1, 0.73)	0.69
ICAM-1, ng/mL	264.7 (227.4, 301.9)	259.5 (220.3, 298.8)	5.12 (-49.0, 59.3)	0.82
VCAM-1, ng/mL	805.9 (743.4, 868.5)	815.1 (749.2, 881.1)	-9.19 (-100.3, 81.9)	0.84
Oleic acid, umol/mL	406.2 (355.4, 457.0)	411.6 (358.1, 465.1)	-5.40 (-79.3, 68.5)	0.88
Weight (kg)	75.7 (73.2, 78.1)	75.9 (73.4, 78.5)	-0.29 (-3.83, 3.24)	0.86
Body-mass index, kg/m2	26.3 (25.2, 27.3)	26.2 (25.1, 27.3)	0.12 (-1.39, 1.65)	0.87
Waist circumference (cm)	92.7 (90.6, 94.8)	92.7 (90.4, 94.9)	0.05 (-2.99, 3.11)	0.97
Waist to hip ratio	0.93 (0.91, 0.94)	0.92 (0.91, 0.94)	0.006 (-0.02, 0.03)	0.59
Waist to height ratio	0.55 (0.53, 0.56)	0.55 (0.54, 0.56)	-0.002 (-0.02, 0.01)	0.77
Primary outcome per-protocol population				
LDL cholesterol, mg/dL	67.2 (60.3, 74.2)	70.1 (62.6, 77.5)	-2.83 (-13.1, 7.38)	0.58
Primary outcome sensitivity analysis ITT population				
LDL cholesterol, mg/dL	66.2 (61.7, 70.8)	70.2 (60.3, 80.2)	-4.0 (-6.8, 14.9)	0.47

*Data are least square means and 95% confidence intervals. †Intention to treat. ‡ Homeostasis model assessment

its safety and feasibility, similar to the findings of the recently published ENABLE pilot trial [29].

Our study has several important limitations. While patients and investigators were not blinded to the intervention, the risk of bias was mitigated by blinded laboratory analyses. The low-fat diet group's lower adherence to prescribed levels may have been influenced by their awareness of being in the control group. Like the CORDIOPREV study, ADD-SPISE was a secondary prevention trial where ethical considerations required healthy diets for both groups, making it challenging to maintain a control group, especially given the cultural appeal and

Table 5 Adverse events

	Mediterranean diet *n* = 103	Low-fat diet *n* = 97
Any serious adverse event*	11 (10.7%)	11 (11.3%)
Recurrent stroke	2 (1.9%)	2 (2.1%)
Acute myocardial infarction or coronary revascularization	0 (0%)	1 (1.3%)
Other cardiovascular	5 (5.4%)	1 (1.3%)
Gastrointestinal	1 (0.9%)	1 (1.3%)
Infections	1 (0.9%)	2 (2.1%)
Neurological	1 (0.9%)	0 (0%)
Other serious adverse event	1(0.9%)	4 (4.4%)
Any nonserious adverse event	35 (34%)	27 (27.8%)
Gastrointestinal	20 (19.4%)	21 (21.6%)
Neurological	11 (10.7%)	3 (3.1%)
Infections	2 (1.9%)	2 (2.1%)
Cardiovascular	2 (1.9%)	0 (0%)
Other nonserious adverse event	0 (0%)	1 (1.3%)

*Data are n (%). Additional information on adverse events is provided in the additional material

clinical guidelines favoring MeDi over a low-fat diet for secondary prevention [23]. The adaptation of the MeDi to include high avocado consumption may limit its applicability in regions with less access to or preference for avocados, and an additional limitation to its external validity is the fact that this was a single-center study. Additionally, both diet groups improved their scores on the 14-point MeDi screener from low to medium or high adherence, potentially reducing the observed effect of the intervention. Most data on the impact of MeDi on cardiovascular and metabolic outcomes compare high adherence (MEDAS score ≥ 8) to lower scores, but in our trial, both groups met the medium or high adherence criteria [30]. Another potential limitation is the use of high-dose statins in both groups, possibly causing a floor effect that limits further LDL-C reduction, which is typically achieved by adding nonstatin medications to high-risk patients [31]. High-intensity nutritional monthly coaching and an intervention that lasted only 3 months limit the external validity of the trial, as this is expensive and adherence tends to decrease over longer periods [29]. Another limitation is the short duration of the intervention; 3 months may have been insufficient to observe a significant change in the main outcome, as suggested for diet trials. Furthermore, confounders commonly found in nutritional clinical trials, such as ethnicity, genotype and nutritional deficiencies, were not studied and cannot be ruled out as having a residual confounding effect not accounted for in this study [32].

The ADD-SPISE trial results are clinically significant, showing that both diet interventions were safe, feasible, and acceptable for patients with recent IS, reducing their LDL-C levels beyond the effect of statins, and should be used as part of the secondary prevention recommendations in these patients. These findings highlight the potential health benefits of incorporating avocados into MeDi as a dietary intervention after IS and suggest further exploration in MeDi research. Future trials should assess similar but longer-lasting interventions and investigate the therapeutic benefits for clinically relevant outcomes in stroke patients.

Conclusion

The results of this trial provide evidence regarding the effects of these diets on the lipid profile and other cardiometabolic risk factors, suggesting that after 3 months, an avocado-based MeDi decreases LDL-C similarly to a

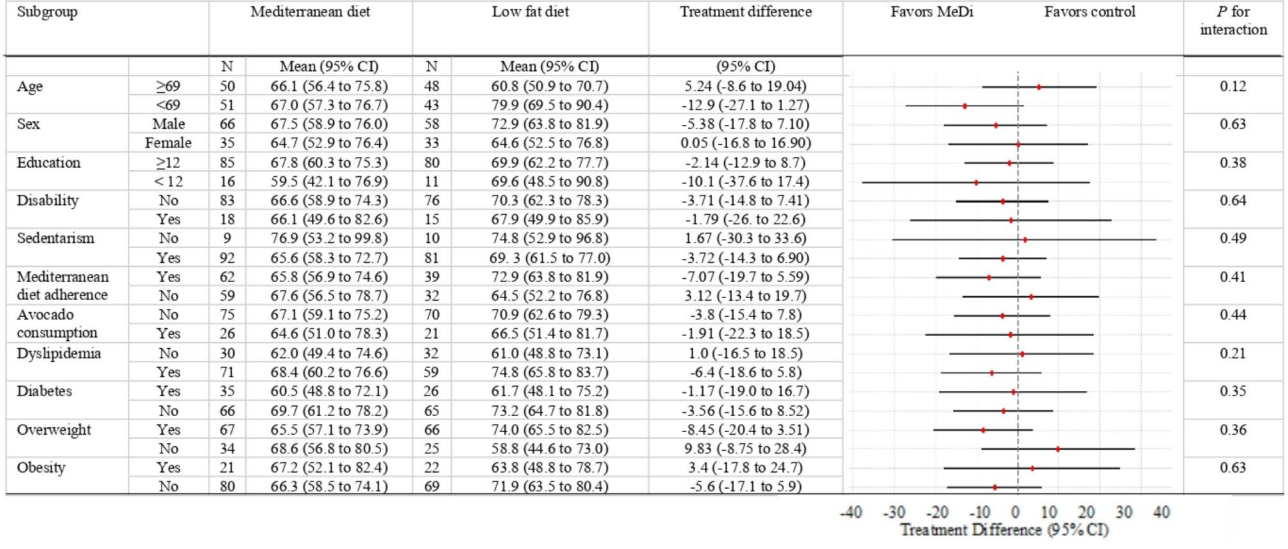

Fig. 2 Subgroup analysis of LDL-C

low-fat diet and could be recommended for all patients with recent IS. There is still only a moderate level of evidence from secondary prevention randomized clinical trials to strongly recommend a MeDi over a low-fat high-fiber diet after a recent ischemic stroke. Large phase III randomized clinical trials should investigate the effects of longer dietary interventions in the prevention of stroke recurrence and other relevant cardiovascular clinical endpoints.

Abbreviations

ADD-SPISE	Avocado-Based Mediterranean Diet on Serum Lipids for Secondary Prevention after Ischemic Stroke
IS	Ischemic stroke
LDL-C	Low-density lipoprotein cholesterol
MeDi	Mediterranean diet
CVD	Cardiovascular Disease
BMI	Body mass index
WC	Waist circumference
MUFAs	Monounsaturated fatty acids
MEDAS	Mediterranean Diet Adherence Scale
PUFAs	Polyunsaturated fatty acids
RAPA	Rapid Assessment of Physical Activity Questionnaire
ITT	Intention-to-treat
HOMA	Homeostasis model assessment
AE	Adverse events
SAE	Serious adverse events
IQR	Interquartile range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02454-4.

Supplementary Material 1

Acknowledgements

We thank the patients who participated in the trial and their relatives and the clinical and research staff from Clínica Alemana de Santiago. We thank Mrs. Olenkha Cepeda, librarians, who performed the systematic review.

Author contributions

VO and PL performed the literature search and designed the study. PvG, CV, PP, BB, PD, EM, VN, MG, PB, AG and PG acquired the data. All the authors interpreted the data. GC performed the statistical analysis. PRC and VV analyzed the laboratory data. VO and PL wrote the first draft of the manuscript. All the authors critically revised the draft and gave final approval for its publication. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the data were included.

Funding

This study is funded by the Agencia Nacional de Investigación y Desarollo (ANID) through the Fondo Nacional de Ciencia y Tecnología (FONDECYT regular N° 018/FONDECYT/882) grant number 1181333.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from Universidad del Desarrollo, Clínica Alemana de Santiago Scientific Ethics Committee (ID 2018–43) for the first protocol and its amendments. All patients or their next of kin provided written informed consent to participate in the trial.

Consent for publication

Not applicable.

Competing interests

VO reports receiving research funding from Clínica Alemana de Santiago and ANID-Fondecyt Regular 1181333 during the conduct of the study and a research grant from Boehringer Ingelheim for the RECCA registry outside the submitted work.PL reports research support from Clínica Alemana and Boehringer Ingelheim. Research grants from Clínica Alemana de Santiago during the conduct of the study, personal fees from Boehringer Ingelheim, and a Chilean Government research grant (ANID) for the ÑANDU project outside the submitted work. VN reports receiving an educational grant from Boehringer Ingelheim. PC, VV, PvG, CV, PP, BV, PD, AG, GC, EM, MG, and PB report no conflicts of interest.

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Received: 30 September 2024 / Accepted: 29 January 2025
Published online: 04 February 2025

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